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CONTENTS

NUMBER 1

PAGE

A remarkable and hitherto undescribed Muscular Lesion occurring in Sprue. By Byrom Bramwell, with Pathological Report by Robert Muir . . 1

On Anaemia with Enlargement of the Spleen, particularly the 'family' form. By John Cowan 11

On the Excretion of Leucin and Tyrosin in two cases of Cardiac Liver. By J. Dixon Mann 25

Additional Observations on Microbic Cyanosis. By G. A. Gibson . . . 29

On Suprarenal Sarcoma in Children with Metastases in the Skull. By Robert Hutchison. With Plates 1–3 33

Abnormal Inception of the Cardiac Rhythm. By James Mackenzie. With Plates 4–9 39

On Haematoporphyrinuria not due to Sulphonal. By T. K. Monro . . . 49

On multiple Hereditary Telangiectases with recurring Haemorrhages. By William Osler. With Plates 10, 11 53

A Note on a ready method of Measuring the Venous Pressure without a Manometer. By George Oliver 59

A Compressed-air Haemomanometer. By George Oliver. With Plate 12 . 60

On the Excretion of Creatinin and Uric Acid in some Diseases involving the Muscles. By E. I. Spriggs. With Plate 13 63

Leukanaemia: its relation to Leukaemia and Pernicious Anaemia. By J. H. Drysdale 89

A Clinical Sphygmomanometer yielding absolute records of the Arterial Pressure. By G. A. Gibson. With Plates 14–19 103

The Association of Physicians of Great Britain and Ireland 107

NUMBER 2

The Pathology of the Cerebro-Spinal Fluid derived from Lumbar Puncture. By J. Graham Forbes. With Plate 20 109

A Study of certain Reflexes in Scarlet Fever. By C. Rolleston . . . 117

The Extra-Systole: A Contribution to the Functional Pathology of the Primitive Cardiac Tissue. Part I. By James Mackenzie 131

The Parathyroid Glands: Part I. Their Function in Relation to the Thyroid Gland. By David Forsyth. With Plates 21–24 150

A contribution to the knowledge of the Action of Digitalis on the Human Heart. By Alexander G. Gibson 173

The Heart in a case of Stokes-Adams Disease. By Alexander G. Gibson. With Plate 25 182

Cervical Ribs and their relation to Atrophy of the Intrinsic Muscles of the Hand. By H. Lewis Jones. With Plates 26, 27 187

An undescribed form of Dwarfism associated with a Spatulate Condition of the Hands. By J. H. Drysdale and W. P. Herringham. With Plates 28–31 193

On Ochronosis: Report of a Case. By Edgar Reid. The Clinical Features. By William Osler. The Urine. By A. E. Garrod. With Plate 32 . 199

Critical Review: Recent Work on Mediterranean Fever. By J. W. Eyre . 209

The Association of Physicians of Great Britain and Ireland 223

NUMBER 3

A Contribution to the Subject of Rheumatism, based upon a Study of 52 Cases in Children under Five Years of Age, and an Analysis of 100 Cases of Fatal Suppurative Pericarditis in Childhood. By F. J. Poynton . . 225

Chloroma and Acute Lymphatic Leukaemia, with an Account of Four Cases, and a Discussion of the Pathology of the Diseases. By C. H. Treadgold. With Plate 33 239

LIBRARY
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SCHOOL OF MEDICINE

PAGE

The Parathyroid Glands: Part II. Their Pathology in Man. By David Forsyth 287

Persistent Hereditary Oedema of the Legs with Acute Exacerbations: Milroy's Disease. By W. B. Hope and Herbert French. With Plates 34, 35 . 312

The Inheritance of Certain Human Abnormalities. By A. M. Gossage . . 331

Critical Review: Caisson Disease. By A. E. Boycott 348

NUMBER 4

The Direct Inspection of the Gastric Mucous Membrane. By H. S. Souttar and Theodore Thompson. With Plates 36–38 375

The Clinical Bearing of Cutaneous Tenderness on various acute Abdominal Disorders, especially Appendicitis. By Henry Robinson 387

On the Origin of Endogenous Uric Acid. By E. P. Cathcart, E. L. Kennaway, and J. B. Leathes 416

The Respiratory Movements in Hemiplegia: A case with Tracings showing the movements of the two sides, and the peculiar effects of Coughing, and a Cyrtometer tracing showing peculiar changes in the shape of the paralysed side of the Thorax. By Samuel West 448

Primary Malignant Disease of the Vermiform Appendix. By Robert Graham Elwell. With Plate 39 454

On Pads on the Finger-joints. By W. Hale White. With Plates 40–42 . 479

The Extra-Systole: A Contribution to the Functional Pathology of the Primitive Cardiac Tissue. Part II. By James Mackenzie 481

INDEX OF CONTRIBUTORS

BOYCOTT, A. E. Critical Review: Caisson Disease 348

BRAMWELL, B. A remarkable and hitherto undescribed Muscular Lesion occurring in Sprue. With Pathological Report by Robert Muir . . 1

CATHCART, E. P. On the Origin of Endogenous Uric Acid 416

COWAN, J. On Anaemia with Enlargement of the Spleen, particularly the 'family' form 11

DRYSDALE, J. H. Leukanaemia: its relation to Leukaemia and Pernicious Anaemia 89

——— An undescribed form of Dwarfism associated with a Spatulate Condition of the Hands. With Plates 28–31 193

ELWELL, R. G. Primary Malignant Disease of the Vermiform Appendix. With Plate 39 454

EYRE, J. W. Critical Review: Recent Work on Mediterranean Fever . . 209

FORBES, J. G. The Pathology of the Cerebro-Spinal Fluid derived from Lumbar Puncture. With Plate 20 109

FORSYTH, D. The Parathyroid Glands: Part I. Their Function in Relation to the Thyroid Gland. With Plates 21–24 150

——— The Parathyroid Glands: Part II. Their Pathology in Man . 287

FRENCH, H. Persistent Hereditary Oedema of the Legs with Acute Exacerbations: Milroy's Disease. With Plates 34, 35 312

GARROD, A. E. On Ochronosis: The Urine. With Plate 32 199

GIBSON, A. G. A contribution to the knowledge of the Action of Digitalis on the Human Heart 173

——— The Heart in a case of Stokes-Adams Disease. With Plate 25 182

GIBSON, G. A. Additional Observations on Microbic Cyanosis . . . 29

——— A Clinical Sphygmomanometer yielding absolute records of the Arterial Pressure. With Plates 14–19 103

PAGE

GOSSAGE, A. M. The Inheritance of Certain Human Abnormalities . . . 331

HERRINGHAM, W. P. An undescribed form of Dwarfism associated with a Spatulate Condition of the Hands. With Plates 28–31 193

HOPE, W. B. Persistent Hereditary Oedema of the Legs with Acute Exacerbations: Milroy's Disease. With Plates 34, 35 312

HUTCHISON, R. On Suprarenal Sarcoma in Children with Metastases in the Skull. With Plates 1–3 33

JONES, H. L. Cervical Ribs and their relation to Atrophy of the Intrinsic Muscles of the Hand. With Plates 26, 27 187

KENNAWAY, E. L. On the Origin of Endogenous Uric Acid 416

LEATHES, J. B. On the Origin of Endogenous Uric Acid 416

MACKENZIE, J. Abnormal Inception of the Cardiac Rhythm. With Plates 4–9 39

———— The Extra-Systole: A Contribution to the Functional Pathology of the Primitive Cardiac Tissue. Part I 131

———— The Extra-Systole: A Contribution to the Functional Pathology of the Primitive Cardiac Tissue. Part II 481

MANN, J. D. On the Excretion of Leucin and Tyrosin in two cases of Cardiac Liver 25

MONRO, T. K. On Haematoporphyrinuria not due to Sulphonal . . . 49

OLIVER, G. A Note on a ready method of Measuring the Venous Pressure without a Manometer 59

———— A Compressed-air Haemomanometer. With Plate 12 . . . 60

OSLER, W. On multiple Hereditary Telangiectases with recurring Haemorrhages. With Plates 10, 11 53

———— On Ochronosis: The Clinical Features. With Plate 32 . . 199

POYNTON, F. J. A Contribution to the Subject of Rheumatism, based upon a Study of 52 Cases in Children under Five Years of Age, and an Analysis of 100 Cases of Fatal Suppurative Pericarditis in Childhood . . . 225

REID, E. On Ochronosis: Report of a Case. With Plate 32 . . . 199

ROBINSON, H. The Clinical Bearing of Cutaneous Tenderness on various acute Abdominal Disorders, especially Appendicitis 387

ROLLESTON, C. A Study of certain Reflexes in Scarlet Fever . . . 117

SOUTTAR, H. S. The Direct Inspection of the Gastric Mucous Membrane. With Plates 36–38 375

SPRIGGS, E. I. On the Excretion of Creatinin and Uric Acid in some Diseases involving the Muscles. With Plate 13 63

THOMPSON, T. The Direct Inspection of the Gastric Mucous Membrane. With Plates 36–38 375

TREADGOLD, C. H. Chloroma and Acute Lymphatic Leukaemia, with an Account of Four Cases, and a Discussion of the Pathology of the Diseases. With Plate 33 239

WEST, S. The Respiratory Movements in Hemiplegia: A case with Tracings showing the movements of the two sides, and the peculiar effects of Coughing, and a Cyrtometer tracing showing peculiar changes in the shape of the paralysed side of the Thorax 448

WHITE, W. HALE. On Pads on the Finger-joints. With Plates 40–42 . . 479

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A REMARKABLE AND HITHERTO UNDESCRIBED MUSCULAR LESION OCCURRING IN SPRUE, WITH NOTES OF A CASE OF PECULIAR (? MYOPATHIC) MUSCULAR ATROPHY IN WHICH SOMEWHAT SIMILAR CHANGES WERE PRESENT

By BYROM BRAMWELL, M.D., F.R.C.P.Ed.

WITH PATHOLOGICAL REPORT BY

Professor ROBERT MUIR, M.D., F.R.C.P.Ed.

The object of this paper is to direct attention to certain alterations in the voluntary muscles which we have found in two cases of sprue—the only cases of the disease which we have had the opportunity of examining post-mortem. These muscular changes have not, so far as we are aware, been previously described; but we venture to think they will probably be found in other cases of the disease in which the muscles are, as they were in this case, extremely atrophied.

In both of the cases which we have had the opportunity of studying, the voluntary muscles throughout the body were atrophied in quite a remarkable degree. During life the condition exactly resembled that characteristic of the advanced stage of myopathic muscular atrophy. In neither of the cases was there any paralysis, but merely profound muscular weakness proportionate to the muscular atrophy; there were no fibrillary twitchings; the electrical reactions were not noted.

In the first case, in which we were able to make a complete post-mortem examination, the peripheral nerves were normal in every respect; in the second case the peripheral nerves were not examined.

The portions of the voluntary muscle which were submitted to microscopical examination showed, in both cases, similar changes. These changes were much more marked in the first than in the second case. They consisted of great proliferation of the nuclei of the sarcolemma, which in places were enormously enlarged, and degenerative changes in the muscular fibres. In places the muscular fibres had apparently been completely absorbed by the enlarged nuclei, the degenerated remains representing the remains of muscular fibres. In the second case, there appeared to be some increase of the inter-

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muscular connective tissue. This seemed to be the result of the muscular atrophy, and not its cause. There was no lipomatosis.

It is probable, we think, that the muscular changes were due to the action of some toxin absorbed from the intestine.

CASE I.—*Typical sprue occurring in a man, aged* 67, *of two years' duration; great intestinal distension; frequently recurring diarrhoea; occasional vomiting; profound anaemia; oedema of the feet; extreme muscular atrophy; petechial haemorrhages shortly before death; extremely rapid post-mortem decomposition.*

CLINICAL REPORT BY DR. BYROM BRAMWELL.

A. B., aged 67, was seen on February 24, 1895, suffering from sprue.

Previous history.—Previous to the development of the disease the patient was a strong, robust, muscular man, weighing 15½ stone. The disease commenced in Singapore a year before the patient came under observation, and had persisted since. Some months before he was seen he came to Scotland; he had resided in Edinburgh since that date.

Condition when seen.—The patient was extremely debilitated, markedly emaciated, and profoundly anaemic; there was some oedema of the feet. He looked as if he were suffering from pernicious anaemia or advanced malignant disease.

The tongue was clean and smooth. The abdomen was markedly distended, the distension being apparently due to the accumulation of gas in the intestines. Diarrhoea occurred several times a day; it was not attended with pain. The attacks of diarrhoea were preceded by powerful vermicular movements of the intestine, but not by noise or rumbling. The motions were very copious, watery, pale in colour, and sometimes frothy and fermented; the evacuations were usually attended with the passage of much flatus. Vomiting frequently occurred. The vomited matters were very copious and watery; the attacks of vomiting usually occurred with great suddenness. The patient stated that on more than one occasion the act of vomiting occurred when he was sitting before the fire, and the watery discharge, which was suddenly expelled, was so copious that it put out the fire.

On microscopical examination the blood showed no changes suggestive of pernicious anaemia. The red blood corpuscles numbered 2,400,000 per cubic millimetre; the haemoglobin was 34 per cent. The red corpuscles were perfectly normal in size and shape; there was no poikilocytosis. The white corpuscles were not markedly increased in number, and were normal in character.

The urine did not contain albumin. The heart and other organs, with the exception of the stomach and intestine, appeared to be normal.

Treatment.—The patient was advised to restrict himself to a milk diet, and to take salicylate of bismuth and arsenic.

Subsequent progress of the case.—March 17, 1895.—The patient looked rather better, was slightly less anaemic; the diarrhoea was less frequent and less urgent in character, the motions were about four a day; he had been keeping almost entirely to a milk diet. The patient stated that he only took the arsenic for a day or two as he thought it made the diarrhoea worse. He was to try it again, also to continue taking the salicylate of bismuth with small doses of laudanum.

December 14, 1895.—After the patient was last seen he went to the Highlands for several months. For a time he had improved slightly, but during the last three or four months he had got much weaker and thinner. In six months he had lost 4 st. 2 lb. in weight. The diarrhoea still continued. The patient's appetite was voracious, he had a craving for everything that is indigestible so long as it is very 'tasty'; latterly he had not dieted himself in any way, but had taken anything and everything that he fancied. The whole of the fat seemed to have disappeared from the body. The voluntary muscles were extremely emaciated. The patient's condition resembled that characteristic of the advanced stage of myopathic muscular atrophy. There was no paralysis, the knee-jerks were present and active, there were no fibrillary twitchings. The patient was advised to recommence the arsenic, together with iron and bone marrow.

January 24, 1896.—Patient was very feeble and looked exceedingly ill. The diarrhoea was again very troublesome. Several minute petechial haemorrhages were present on the skin, on the tongue, and on the buccal mucous membrane. He was advised to go to bed and to restrict himself to a purely milk diet.

January 29, 1896.—The patient was still looking extremely ill, and felt very weak. The diarrhoea was very much better; for the last two or three days there had been only one motion a day; the motions were pulpaceous in consistence and yellow in colour. The abdomen was greatly distended with flatus.

February 19, 1896.—Patient was suffering from an attack of acute bronchitis; there was a great deal of frothy expectoration which had on more than one occasion been tinged with blood. The temperature had once risen to 102°.

February 23, 1896.—Patient died somewhat suddenly.

Pathological Report by Professor Robert Muir.

The post-mortem examination was made by Professor Muir, in the presence of Dr. Byrom Bramwell, on February 24, 1896, at 10.15 a.m.

The body showed very extreme emaciation and muscular atrophy. There were signs of advancing decomposition over the abdominal wall.

There were one or two adhesions over the *lungs*, but otherwise the serous cavities were quite normal. Both lungs were emphysematous in

front, and oedematous posteriorly, but otherwise normal. The *heart* showed no abnormality beyond pallor and softening of the myocardium, along with some atrophy.

The *peritoneum* was normal. The *coils of intestine* showed a remarkable appearance. They were somewhat distended, and the walls were extremely thin and semi-transparent, so that particles in the interior were distinctly seen. They had also a very anaemic appearance. The change affected both the small and large intestines, but the former in somewhat greater degree. On opening the intestines, the mucous membrane appeared extremely atrophied, anaemic, and comparatively smooth on the surface, the valvulae conniventes being distinctly less pronounced than usual.

The *stomach* was somewhat small in size; its wall showed a corresponding change to that which was present in the intestine, though in a less marked degree. The *liver* was distinctly atrophied, of a brownish colour, and showed some venous congestion. The *spleen* was of normal size, the capsule wrinkled, and there was distinct increase of the supporting stroma; the Malpighian bodies could be with difficulty distinguished. The *kidneys* showed nothing abnormal beyond slight general atrophy. The *brain* was in an advanced stage of decomposition.

We consider that the appearances found corresponded with those described in cases of sprue, the atrophic change in the intestines being of quite an extreme degree.

Since a marked atrophy of all the voluntary muscles had been a conspicuous feature during life, portions of the muscles and peripheral nerves were kept for microscopic examination. The muscles generally were much atrophied. They were somewhat soft, and were both paler and more transparent-looking than normal. The microscopic examination showed a very remarkable change.

Microscopic Examination of the Organs and Tissues.

Small intestine (the examination was somewhat interfered with by the degree of putrefactive change present; thus the superficial part of the mucous membrane stained very feebly, and it was not possible to be certain whether there was some pre-existing necrotic change).—The following appeared to be the chief changes. There was extreme atrophy of all the coats, the total thickness of the wall not exceeding about a third of the normal intestine. The villi were very stunted, and had lost their epithelium; the lymphoid cells of the adenoid tissue were very scanty, and scarcely stained with haematoxylin. Lieberkuhn's glands were much shortened, and were devoid of epithelium except at their lower end, the surviving cells being irregular in shape. The interstitial adenoid tissue and the solitary glands seemed to have disappeared. The muscularis mucosae could be readily distinguished, and its fibres were somewhat separated. The submucous coat was constituted by a thin layer of oedematous

fibrous tissue. Both muscular coats were much atrophied, and some of the fibres had lost their nuclei.

The *large intestine* showed a similar condition, though the degree of atrophy was scarcely so great. Lieberkuhn's glands were less destroyed, but were much distorted in their arrangement; their epithelium was irregular, granular, and in the superficial parts desquamated. Here also there was much atrophy of the lymphoid tissue. The other coats showed a similar condition to that present in the small intestine. There were organisms of all kinds on the surface of the mucous membrane, and also in its superficial parts.

Muscles.—The portion examined was from the biceps. Its condition was of a striking character. At places many of the fibres were of nearly normal size, some retaining their transverse striation and some being of homogeneous aspect. Here and there multiplication of the nuclei of the sarcolemma could be seen. These nuclei had become at many places greatly enlarged, and assumed a peculiar convoluted appearance, this change being accompanied by an absorption of the muscle substance. The growth of the nuclei could be seen to have reached an extreme degree, so that a fibre might be in great part covered by them. A large proportion of the fibres, moreover, were in an extremely atrophied condition, more or less homogeneous, of irregular thickness, and partially covered with proliferated nuclei. All stages could be seen, down to complete disappearance of the fibre, in which case its position was marked by a collection of nuclei in a more or less degenerated condition. At places merely a granular material, staining of a peculiar bluish tint with haematoxylin, could be seen, but I think there can be little doubt that it was merely the remains of degenerated nuclei. In parts where the change was most advanced, the muscle fibres were mere lines, in great part covered by the proliferated nuclei or their remains; at such a stage there was considerable thickening of the interstitial connective tissue.

The *nerve* going to the muscle was examined, but showed nothing abnormal. The medullary sheaths were wonderfully well preserved, and appeared quite healthy, as also did the axis cylinders.

I consider that the microscopic appearances of the muscle indicate that its substance was undergoing degeneration as the result of the action of some toxic substance in the blood, possibly absorbed from the intestine, and that this degeneration was followed by proliferation and remarkable enlargement of the sarcolemma nuclei, these acting, in fact, as phagocytes and absorbing the muscle substance. The change which was present in the nuclei in this case occurs to a certain extent in some other pathological states of muscles, but I have never seen it even approaching such a degree as in this case. The picture which this case presented is, in my experience, quite unique. The general result of the microscopic examination confirms the opinion that the case was one of sprue, and the condition just described indicates the importance of examining the muscles in this disease. (In Dr. Thin's book there is no mention of histological changes in the muscles.)

CASE II.—*Typical sprue of ten years' duration; extreme emaciation and muscular atrophy; death.*

X. Y., aged 40, was seen by B. B., in consultation with Dr. James Wilson, on May 4, 1899, suffering from sprue in its most advanced stage.

History.—The disease commenced some ten years ago, and has continued, with periods of improvement, ever since.

Dr. David Galloway, under whose care the patient was when the disease commenced, and while he resided abroad, kindly sent me, after the patient's death, the following account of the early history of the case:—

'His family history is unexceptionable, as is also his personal history. He arrived in the Straits in 1887, a perfectly healthy man; in fact, an athletic, well set-up young fellow. During his stay there, before the symptoms of sprue manifested themselves, he led a most careful life; especially in the matter of diet, on which he held very sensible opinions, he was most circumspect. Within eighteen months of his arrival he had unmistakable sprue; his case was a most acute one; in fact, out of some sixty cases which I have watched and noted carefully during the last fourteen years, there are only one or two others of equal acuteness. His symptoms were classical; beginning with the usual "dyspeptic" symptoms, they gradually became those of typical sprue, viz. (*a*) recurrent attacks of inflammation of the whole buccal cavity and tongue, leaving the parts painful and mostly denuded—each of these attacks was accompanied by a slight rise in temperature; and (*b*) severe diarrhoea.

'The diarrhoea, which is not an integral part of the disease, but which is nearly always present in Europeans, was very marked in his case, so much so as to cause a rectal prolapse.

'He was fed on a mixed raw meat and milk diet, and was treated with rectal injections of nitrate of silver. On this diet he always improved.

'In 1892 he went to Shanghai to consult a quack of some reputation in this disease, and returned scarcely so well as when he left. He then proceeded to Europe, returning much improved in 1894. He was in the Colony only a few weeks, when his disease asserted itself again most virulently; eventually he left for good in September, 1894.'

Dr. James Wilson, under whose care the patient was after his return to Scotland in the year 1894, has kindly given me the following notes of the condition:—

'I saw Mr. *X. Y.* professionally about four years ago. He had been feeding on mixed diet for some time, and had been losing flesh. He always did so after being on mixed diet for some time. He was put to bed and given milk exclusively, and he began to improve as regards his stools and also generally, again putting on weight. He never had what you could call diarrhoea, but loose stools three or four times a day. He always tried to keep his stools firm, and would keep on any diet so long as his stools kept firm. Whenever he got up to a fair weight, after a milk diet, he would add fruit in the shape of bananas, and then gradually slip into a mixed diet; he would continue the mixed diet till his stools became loose and he was becoming thin. In this way he rung the changes of diet till the end.'

'Bananas suited him, and he always improved in the summer when he could get plenty of strawberries. (Thin, I see, has made some observations about this fruit.)

'When I saw him first his tongue was red and clean, its epithelial covering being smooth and thin. His skin was harsh, dry, and scaly, especially when

he was on mixed diet and getting thin; whenever he put on flesh again his skin became slightly more moist. The hair was thin and dry. His abdomen was always much distended. Warm weather always helped him; he was always best in summer in the warm weather, when he could get plenty of strawberries, as I mentioned before. He had great faith in the strawberries, and used to say whenever he could get them he would be all right.

'He went down to Penzance in the winter of 1897, in a fairly plump condition for him, but when he came back in the spring of 1898 he was a walking skeleton, a condition from which he never improved. Nothing would put flesh on him after that. He maintained his strength fairly well during the summer and autumn of 1897; after this he gradually got weaker till you saw him in the spring of this year (1899).'

Condition on May 4, 1899.—The patient was profoundly emaciated; all the fat appeared to have disappeared from the surface of the body, and the muscles were all extremely atrophied. There was no paralysis, no affection of the bladder or rectum (other than the looseness of the bowels due to the sprue), and no sensory defects. The lips were somewhat pale, but the patient was not, in any notable degree, anaemic, the conjunctivae being well coloured. The abdomen was greatly swollen and tympanitic; on palpating it one was reminded of the sensation produced when one palpates a swollen and decomposing corpse. Several boils were present on the knees and adjacent parts of the legs; but there were no bed-sores and no petechiae. The patient, who was mentally bright, stated that he felt the cold very much.

Result.—The patient died on May 20, 1899.

The microscopic examination of the muscles.—A complete post-mortem was not made, but the late Dr. Hunter Mackenzie, who was interested in the case, removed and sent me, preserved in Müller's fluid, a portion of the biceps muscle.

Professor Robert Muir kindly made the microscopic examination, and found exactly the same changes in the muscle, though less marked in degree, which were present in the first case. In this (the second) case there appeared to be some increase of the intermuscular connective tissue; it seemed to be the result of the muscular atrophy, not its cause; there was no lipomatosis.

Remarks.—The muscular changes which we have found in these two cases of sprue have not, so far as we have been able to ascertain, been previously described in that disease. They seem to us to suggest the poisoning of the muscle by some toxin probably absorbed from the intestine.

The enormous increase of the nuclei, and the destruction of the muscle tissue, which apparently resulted therefrom, are very remarkable, and have not, so far as we know, been met with in the same degree either in sprue or in any other disease. A somewhat similar change in the nuclei, though much less marked in degree, was present in a remarkable case of myopathic muscular atrophy which came under the notice of one of us (Dr. B. B.) in the year 1896. It is noteworthy that in that case the only cause which suggested itself for the extensive muscular wasting was chronic poisoning by tobacco taken in the form of chewing—an observation which perhaps lends

some support to the view which we have advanced that in the two cases of sprue the remarkable muscle changes were probably due to some form of intoxication. The details of this case of muscular atrophy are as follows:—

Case of Extreme Muscular Atrophy in which somewhat similar changes to those described in the two preceding cases of Sprue were found after death.

Clinical Report by Dr. Byrom Bramwell.

C. D., married, aged 64, was seen on September 2, 1896, complaining of progressive muscular weakness, loss of flesh and muscle, occasional dyspepsia, and some cough.

Previous history.—The patient, who had been an active, healthy man, and had lived in a very healthy country district, began to lose flesh and strength in October, 1895. The muscular weakness and emaciation gradually progressed until I saw him on September 2, 1896.

Condition when seen.—The patient was extremely emaciated; all the fat seemed to have disappeared from the surface of the body; the muscles generally were markedly atrophied; he then weighed 9 st.; before his illness commenced—in October, 1895—he weighed 13 st. The muscular weakness was so great that the patient could not raise himself in bed to be examined; but when he was assisted to his feet he managed to stand and walk. There was no paralysis; the knee-jerks were absent; there were no fibrillary twitchings, no affection of the bladder or rectum, and no disturbance of sensation.

The patient complained of pain on pressure over the bones, especially over the lower end of the sternum, the superior iliac crests, and the spines of the vertebrae, but nothing abnormal could be seen in these situations. Throughout the course of his illness the patient had at times been dyspeptic, but when seen on September 2, 1896, the stomach seemed normal. There was no marked anaemia. The organs all seemed to be healthy; the urine was normal.

Diagnosis.—The condition resembled the profound muscular atrophy in the two cases of sprue, which have been previously described, more than anything else that I have seen.

The patient could not account in any way for the development of the muscular weakness and emaciation. His wife stated that for several years past he had been in the habit of chewing tobacco almost continuously; he hardly ever was, she said, without a quid in his mouth. The patient himself said he never swallowed the saliva while 'chewing'. He further stated that he had always been very susceptible to the action of tobacco, and that he had never been able to smoke two pipes straight off in his life. For some months before I saw him he had discontinued chewing in such large quantities.

Progress of the case, February 8, 1897.—The patient was seen again on this date. He thought he had slightly improved under feeding, massage, strychnine, and arsenic. The appetite and digestion were good. He complained of some

pain in the back of the neck and on the crown of the head; also occasionally of pain in the eyeballs.

No visceral disease was to be detected. The muscular weakness was extreme, though he was still able to walk with the help of two sticks, he could not, however, get up from a sitting to a standing position or raise himself in bed. The right calf, at its thickest point, measured 9, the thigh 11, the forearm 7, and the upper arm 6½ inches. His height was 5 feet 10 inches.

May 22, 1897.—The muscular atrophy was even more marked than it was at the time of the last visit. The calf measured 8, the thigh 10½, the forearm 6¾, and the upper arm 6¼ inches. The skin had a greasy feel and look. The feet were swollen. There was no paralysis. The atrophied muscles contracted actively to the faradic current; there were no fibrillary twitchings.

After this date the patient gradually got weaker and weaker, and died on July 27, 1897.

Post-mortem examination made on July 28, 1897, *at* 5 *p.m.*—Decomposition was already far advanced. The vertebral bones were softer than normal; the outer surface of the dura mater was stained of a greenish-red colour by putrefaction; the spinal cord was very soft.

The lumbar and cervical enlargements, a portion of the dorsal cord, and the cauda equina were removed and at once placed in Müller's fluid. Portions of the biceps muscle from the left arm, some muscles of the left forearm and of the ball of the left thumb, were removed, together with the two nerves from the upper arm, the median and another small nerve from the left forearm, and portions of the left external popliteal nerve and of the calf muscles. The calf muscles appeared to be more degenerated than the muscles of the arm and forearm, and were of a brownish-red colour.

The *heart* was markedly atrophied, the muscle being of a yellowish-brown colour and very soft; a portion was removed and placed in Müller's fluid.

The *left pleural cavity* contained a considerable amount of fluid and flakes of lymph, the result of a recent pleurisy. The *lungs* were quite healthy.

The *stomach* and the *other abdominal viscera* were all healthy. The *liver* was somewhat small and fatty; otherwise it was normal. The *spleen* was shrunken, pale, and atrophied. The *kidneys* were congested, showing marked post-mortem changes; otherwise they were healthy.

Microscopic Examination by Professor Robert Muir.

The muscles.—The changes present were of a very striking character. There was extraordinary variation in the size of the fibres; some were distinctly thicker than normal, whilst all sizes down to those about the diameter of a red corpuscle in thickness (or even less) were present.

The larger fibres, as a rule, were well striated, but a few of homogeneous aspect were present. Some showed proliferation of the nuclei of the sarcolemma, the nuclei being arranged for the most part in rows. Splitting of the larger

fibres into numerous smaller fibres could be distinctly followed. Some of the fibres were of unequal thickness.

In the smaller fibres nuclear proliferation was also present; and, though the large majority showed very distinct transverse striation, a few were of homogeneous aspect or even of granular appearance. In these (the degenerated fibres), great enlargement of the sarcolemma nuclei could be seen, the nuclei being pale, with a loose chromatin reticulum, and at places so large as entirely to cover the fibres.

Remarks by Professor Robert Muir.

In this case, then, there was present in a minor degree the same change as in the cases of sprue previously described, i.e. a phagocytic action on the part of the sarcolemma nuclei towards the degenerated muscle substance. This nuclear change was only found, however, here and there. The most marked feature of the case was the large proportion of muscular fibres of very small size interspersed with those of larger size, the striation being strikingly well preserved. Interstitial growth of fibrous tissue was not marked, though a certain degree was present amongst the smallest fibres, where in fact some of these were disappearing altogether. There was practically no lipomatosis.

The walls of the arteries were distinctly thickened. The minute arterioles showed fibroid sclerosis; in those of larger size there appeared to be distinct hypertrophy of the middle coat in addition to some thickening of the intima and adventitia.

Spinal cord.—Sections were examined from the lumbar and cervical enlargements and from the dorsal region. Most of the cells in the anterior cornua were well preserved and their processes very distinct. Some of them showed homogeneous patches in their protoplasm, and some were distinctly granular, this latter condition affecting the processes also. I think that these alterations were probably in part at least post-mortem changes, as there was distinct evidence that the hardening of the cord was not perfect. I consider that there was no evidence of any primary change in the nerve cells. There was no degeneration in the white matter, and no abnormality beyond one or two patches of slight neuroglial thickening in the posterior columns in the cervical region—a change probably of no importance.

The nerve roots and portions of the spinal nerves which were examined also appeared healthy.

From the condition found, I consider that the case belonged to the class of myopathic atrophies.

ON ANAEMIA WITH ENLARGEMENT OF THE SPLEEN, PARTICULARLY THE 'FAMILY' FORM

By JOHN COWAN, M.D., D.Sc.

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The association of anaemia of a severe type and enlargement of the spleen without evident cause has been recognized clinically for many years, and a specific malady, chronic splenic anaemia, is apparently being disentangled from the large group of cases of varied origins which present these two main symptoms. In the present state of matters full clinical records with post-mortem examinations are urgently needed, but isolated observations, even though incomplete, are also desirable, as the disease is comparatively rare and few observers have seen many cases. Two cases of anaemia with splenic enlargement have lately come under my observation, which present some features which do not seem to have been commonly observed.

Case I.

William Turner, aged 21, was admitted into Professor Gemmell's Wards in the Western Infirmary, on December 7, 1903, complaining of a traumatic ulcer on his right leg, and of swelling of the feet of some seven months' duration. Accurate information as to his past history was not available, but he had always been a delicate boy. At the age of 9 his spleen was discovered to be large, and his colour was pale and yellowish; at 12, he was in bed for six weeks with abdominal symptoms, and pain in the splenic region; at 19, he was away from work for several weeks on account of an influenzal attack. He had worked regularly for two years, although he was often very tired and his feet were frequently swollen at night. In July, 1906, he injured his right leg; a small superficial abscess formed and discharged, the wound did not heal, and in consequence he sought admission to hospital.

On examination he was found to be of poor physique, only measuring 5 ft. 2 in. in height, and weighing 6 stone 9 lb.; and he looked more like a boy of 16 than his real age. The sexual organs were immature, and the hair on the pubes, upper lip, and in the axilla was but scanty. He was badly nourished, and his muscles were soft and flabby. He was evidently anaemic, and both skin and mucous membranes were distinctly yellow. His tongue was slightly coated, the teeth were carious and the breath foul-smelling, but he had a fair

appetite and no symptoms of indigestion. The stools were normal in every way. The abdomen was prominent, mainly on account of an enlarged spleen which reached nearly to the iliac crest; the liver also was enlarged, the area of dullness in the vertical nipple line measuring 4½ in.; neither was tender or fixed, and their outlines were distinct. The lymphatic glands in the groin and axilla were slightly enlarged. The temperature was normal. The lungs were healthy. A short systolic murmur was audible at the cardiac apex, but otherwise the heart seemed normal. The urine was dark in colour, of a reddish tint, but did not contain urobilin. The reaction on testing for bile pigments was doubtful, but bile salts were present. No albumin or sugar was found.

During his residence in hospital symptoms were in abeyance, and the ulcer on his leg healed rapidly. His general condition, however, remained unchanged and he left the wards at his own desire.

Blood Examination.

	Red Cells	Haemo-globin	Colour Index	White Cells	Polymorph			Myelo-cytes	Small mono-nuclears	Transitionals and large mononuclears
					Neutro-phil	Eosino-phil	Baso-phil			
Dec. 10, 1903	2,540,000	44 %	·85	5,800	65·5	2	0·5	Occa-sional	24·5	7·5
Jan. 2, 1904	2,240,000	55 %	1·03	5,600						
Jan. 18, „	2,000,000	55 %	1·37	6,500						

Examination of stained films showed a notable variation in the size and shape of the red cells, many very large and very small forms being present. The staining of the stroma was as a rule good, but a few cells showed polychromatophilia. A fair number of nucleated red cells were seen, the minority of which were megaloblasts. The white cell count showed that the mononuclear cells were relatively in excess. Many large lymphocytes were present; one or two myelocytes were found.

Case II.

John Calder, aged 19, was admitted into my wards in the Royal Infirmary on January 22, 1907, complaining of weakness and of breathlessness, of many months' duration. He had always been a delicate boy, and had resided in hospitals on many occasions. At the age of 4½ years he suffered from gastro-intestinal symptoms (vomiting and diarrhoea), which probably did not last for very long, but his belly, feet, and hands became swollen, and he was admitted into the Royal Hospital for Sick Children for a few weeks, suffering from 'anaemia'. At the age of 7 he was again in hospital on account of similar symptoms, and the liver at this time was noted to be rather large, the area of dullness in the vertical nipple line measuring 4½ in. The spleen, however, was not enlarged. At the age of 10 he was again in hospital, suffering from debility and dry pleurisy on the right side, and he was again said to be 'anaemic'. He commenced work as a sheet-iron worker at the age of 15, but at the age of 16 was forced to leave work, and seek admission to the Royal Infirmary on account

of gastric symptoms (pain, flatulence, vomiting, constipation), which lasted for some six months, and were considered to be the result of lead poisoning. He left hospital after a month's residence, and resumed his work, at which he continued until a few days prior to his present admission. His work was heavy, and he was easily made tired and breathless, and he refrained from playing games on this account. The debility and breathlessness gradually increased until they made work impossible, and he again sought admission to the wards.

The patient was found to be poorly developed, only measuring 5 ft. in height, and weighing 7 stone. The skin generally was pale and somewhat yellow in tint, but no pigmentation was present. There was little subcutaneous fat, and his muscles were small and flabby. The pubic hair was scanty, and the right testicle was small: there was no hair in the axilla, and his moustache was only just appearing.

On examination the mouth was found to be very septic, and the tonsils were enlarged, but the tongue was clean, the appetite was good, and no gastro-intestinal symptoms were present; the stools were normal. The spleen was slightly enlarged and could be felt immediately beneath the costal margin, its area of dullness measuring 5½ in. in the axillary line. The area of dullness in the hepatic area measured 4¾ in. in the vertical nipple line. Both liver and spleen were movable and painless, and their margins were distinct. The abdomen otherwise seemed normal. The left heart on admission was slightly dilated, and a systolic mitral murmur was present, but it soon disappeared. The other viscera seemed normal. The urine on admission was dark in colour, acid in reaction, of S.G. 1·016 and contained a trace of albumin, but no sugar, bile, blood, or indican; on subsequent occasions the colour was never abnormal, but the albuminuria persisted. A few minute haemorrhages were seen in the retinae on admission, but they disappeared in a few days.

No symptoms of any kind appeared during his residence in hospital. He was very quiet at first and slept a great deal, but the lassitude soon passed away, and he became even mischievous. When he was dismissed on April 19 he had gained 8 lb. in weight, and felt well in every way.

Blood Examination (Archibald W. Harrington).

	Red Cells	Haemo-globin	Colour Index	White Cells	Polymorph			Myelo-cytes	Small mono-nuclears	Transitionals and large mononuclears
					Neutro-phil	Eosino-phil	Baso-phil			
Jan. 24, 1907	2,000,000	30 %	·75	8,000	50·89	2·13	1·35	2·52	28·34	14·75
Feb. 2, „	2,600,000	50 %	·96	6,000	...	...	...	...	...	...
Feb. 22, „	2,600,000	50 %	·96	6,000	54·8	3·4	·8	1·2	25·8	15
Apr. 19, „	2,880,000	45 %	·79	5,700	56·2	3·3	·2	...	29·8	10·5

On examination of stained films, the red cells showed notable variations in size and shape, many very large forms being present, and some granular degeneration and polychromatophilia were also noted. Nucleated red cells

were numerous, and less than half were megaloblasts. The white cells were not present in abnormal numbers, but a differential count showed that the non-granular cells were relatively in excess, that many large atypical cells of the lymphocyte class, with much protoplasm, appeared, and that some myelocytes were also present.

It is extremely difficult to acquire a proper perspective of a disease so chronic as splenic anaemia. For years, perhaps, the patient may enjoy fair health and be able to follow his usual pursuits; but a time comes when symptoms make their appearance, and it is then that advice is sought. Anaemia becomes extreme, a haemorrhage occurs, or an infective accident; and the essential features of the disease are obscured by the addition of symptoms which are not really due to the primary cause. The cases which I have just described may or may not be examples of splenic anaemia, but they differ in some ways from the average case, and in the meantime may perhaps be left unclassified.

Osler's[1] experience of these cases is perhaps the largest hitherto reported, and I shall consider my own cases on the lines which he has already laid down.

Age.—The average age at the onset of symptoms in Osler's series of fifteen cases was 32·5 years. In Rolleston's[2] collection of thirty-five cases the average age (when seen?) was 32. In one of my cases the spleen was known to be enlarged at the age of 9; in the other the boy was 'anaemic' at 4½. A fair number of cases seem to commence in early life. Symptoms were manifest in one of Osler's cases at the age of 9, and in Rolleston's case at 11. The onset is put at 2 years of age by Collier[3]; 3 by Bovaird[4] (two cases) and Brill[5]; 3–5 and 5–6 by Wilson[6]; 6 by Collier and Hamill[7]; 7 by Gaucher[8], Williamson[9], Springthorpe[10], Wilson (two cases); 8 by Wilson; 10 and 11 (two cases) by Springthorpe; 12 and 13 by Scott[11]; 14 by Summons[12]; 15 by Michell Clarke[13].

Duration.—In both of my cases symptoms had existed for many years, in the first for at least twelve, in the second for fourteen. This is in accordance with the general results, death rarely ensuing early unless from

[1] Osler, W., *Amer. Journ. Med. Sci.*, Phil., 1900, vol. cxix, p. 54; ibid., 1902, vol. cxxiv, p. 751.

[2] Rolleston, H. D., *Clin. Journ.*, London, 1902, vol. xix, p. 401.

[3] Collier, W., *Trans. Path. Soc.*, London, 1895, vol. xlvi, p. 148.

[4] Bovaird, D., *Amer. Journ. Med. Sci.*, Phil., 1900, vol. cxx, p. 377.

[5] Brill, N. E., *Amer. Journ. Med. Sci.*, Phil., 1901, vol. cxxi, p. 375.

[6] Wilson, Claude, *Trans. Clin. Soc.*, London, 1890, vol. xxiii, p. 162; ibid, 1893, vol. xxvi, p. 163.

[7] Hamill, S. M., *Arch. of Ped.*, N. Y., 1902, vol. xix, p. 641.

[8] Gaucher, E., *Thèse de Doctorat*, Paris, 1892.

[9] Williamson, R. T., *Med. Chron.*, Manchester, 1893, vol. xviii, p. 103.

[10] Springthorpe, J. W., and Stirling, R. A., *Lancet*, London, 1904, vol. ii, p. 1013.

[11] Scott, J. A., *Amer. Journ. Med. Sci.*, Phil., 1903, vol. cxxvi, p. 856.

[12] Summons, *Lancet*, London, 1904, vol. ii, p. 1017.

[13] Clarke, J. Michell, *Bristol Med. Chir. Journ.*, 1903, vol. xxi, p. 14.

accidental complications. James'[14] and Gaucher's cases lived for twenty-five years after the splenic enlargement was observed, and one of Wilson's cases for thirty years.

Development.—The arrested development in both of my cases was striking, but it is not surprising, considering the age at which ill-health supervened. In Bovaird's second case the mental development at the age of 13 was defective, and the stature was small. Byrom Bramwell[15] has reported a case of 'Infantilism associated with anaemia and enlargement of the spleen'. The boy at the age of 18 did not look older than nine; he measured 4 ft. 2¾ in., and weighed 4 st. 10¼ lb.; the sexual organs were undeveloped, but he was mentally bright and sharp.

Splenomegaly.—In Osler's cases the splenic enlargement was always notable. The average weight in twelve cases collected by Rolleston was 61 oz. Collier has reported the case of a child whose spleen weighed 4 lb. 2 oz.; the child's total weight was 23 lb. The spleen in Sippy's[16] case weighed 5 lb. 2 oz., and in one of Bovaird's cases 12½ lb. The enlargement may, however, be moderate, as in Bovaird's other case, in Hamill's case, and in two of those reported by Springthorpe. In my first case[17] the splenic enlargement was great; in the second it was moderate.

The Size of the Liver.—The size of the liver seems to be variable. The organ was enlarged in six of Osler's cases, in both of Bovaird's, in Hamill's, Gaucher's, Brill's (2), Sippy's, Scott's (1), Springthorpe's (2), Summons's, Wilson's (3), and Williamson's (1) cases. In one of Osler's cases the liver was smaller than normal. There was no enlargement in six of Osler's cases, in Michell Clarke's, Williamson's (1), Rolleston's, Scott's (1), and Springthorpe's (1) cases. In both of my cases the liver seemed to be slightly enlarged.

Haemorrhagic tendency.—Osler has drawn attention to the frequency with which the haemorrhagic tendency is met with in these cases. Haematemesis, often copious and repeated, occurred in eight of his fifteen cases, while haemorrhage from other sources was less common. Haematemesis occurred in Hamill's, Rolleston's, Williamson's (1), Michell Clarke's, Levison's,[18] Springthorpe's (1) cases; melaena in one of Brill's cases; epistaxis, or haemorrhage from the gums, in Gaucher's, Rolleston's, Williamson's (1), Sippy's, Brill's (2), Summons's cases. In my first case no haemorrhagic tendency was noted; in the second a few small haemorrhages were present at one time in the retinae.

Pigmentation.—Eight of Osler's cases showed some pigmentation of the skin, which was as a rule diffuse. Springthorpe refers to a 'chlorotic' tinge

[14] James, quoted by Osler.

[15] Bramwell, Byrom, *Clin. Studies*, Edinburgh, 1902, vol. ii, p. 354; ibid., 1906, vol. iv, p. 29.

[16] Sippy, B. W., *Amer. Journ. Med. Sci.*, Phil., 1899, vol. cxviii, pp. 428, 570.

[17] Cowan, John, and McClure, J. Campbell, *Brit. Journ. of Children's Diseases*, London, 1906, vol. iii, p. 343.

[18] Levison, C. G., *Annals of Surgery*, London, 1903, vol. xxxviii, p. 671.

in two of his cases; all of Wilson's cases were 'sallow' in complexion; and Brill, Bovaird, Levison, and Scott describe the complexion of their cases as being more or less yellow in colour. Osler and Brill state that arsenic had been administered in some of their cases over long periods, and suggest that the pigmentation may have been due to the drug. Both of my cases had a yellowish coloration of the skin, similar to that met with in cases of pernicious anaemia.

Anaemia.—Full records of the condition of the blood are wanting in many of the cases hitherto recorded; and continuous records over a series of years are only available in three or four cases (Osler, Bovaird, Hamill, Brill). In a disease which is so chronic and not incompatible with fair health over long periods, one would expect to find fairly normal blood during the quiescent stages, and, if haemorrhage had recently occurred, blood reactions suited to the loss, so far as the individual was capable of reacting. A similar state of matters obtains, for example, in pernicious anaemia where blood crises and a megaloblastic reaction may appear and disappear in the different stages of the disease.

Red Cells.—The average red cell count in forty-one cases collected by Osler was 3,425,000, the lowest count numbering 2,187,000, and the highest 5,200,000. Michell Clarke records a count of 1,171,000, Sippy one of 1,740,000, Rolleston, 2,400,000, Scott, 2,440,000, Levison 2,537,000, Bovaird 2,880,000; while three of Springthorpe and Stirling's cases showed counts between 2,250,000 and 2,960,000. In the other cases the counts were above 3,000,000.

Haemoglobin.—The average haemoglobin value in thirteen of Osler's cases was 47%, his lowest count being 25%. In Michell Clarke's case the value, after severe haemorrhage, was only 12%. The colour index is as a rule low, and may be much reduced (·33 Williamson, ·37 Osler), but on the other hand may be above unity (Springthorpe and Stirling 1·4, 1, 1, Scott 1·2).

A megaloblastic reaction is apparently uncommon, though normoblastic crises are not infrequent, but the records on this point are defective. In two of Osler's cases the films showed a few microcytes and megalocytes. Levison records the occasional presence of megalocytes and a few megaloblasts; in Michell Clarke's case the red cells varied greatly in their size; one of Scott's cases showed numerous normoblasts and one megaloblast: while in three of Springthorpe's cases nucleated red cells were numerous and megalocytes were present; in Summons's case megalocytes were numerous.

It is extremely unfortunate that the records as a whole are so defective. So far as they go, however, they show a megaloblastic reaction most frequently in the juvenile cases, the ages in the cases mentioned being, in order, 58, 39, 27, 30, 12, 7, 10, 11, 14, 21, 19.

White Cells.—The white cell count is usually below the normal, the average in fourteen of Osler's cases being 4,520, the minimum being 2,400 and

the maximum 18,720. Variations above normal seem always to be associated with complications, and may, I think, be discarded, a normal or subnormal count being the rule.

Differential counts are as a rule normal, but in a fair number of cases a relative decrease in the neutrophil polymorphs has been recorded. This obtained in five cases of Osler's series, and in Bovaird's (2), Hamill's (2), Dock and Warthin's [19], Sippy's, Brill's (2), Michell Clarke's, Scott's (2), Springthorpe's (1) cases. In several cases the large mononuclears or the large lymphocytes are stated to be relatively increased. One myelocyte was found in Michell Clarke's case.

The condition of the blood in the cases which I have described differs in several respects from that which seems to be the rule in cases of splenic anaemia. A considerable reduction in the number of red cells, with a corresponding loss of haemoglobin and a relatively high colour index; a megaloblastic reaction; leucopenia, with excessive loss of neutrophil polymorphs, and the presence of myelocytes and atypical cells of the lymphocyte class; these are collectively a blood picture which would point away from a diagnosis of splenic anaemia.

A megaloblastic reaction is, in the adult, more or less uncommon, and it is only recognized in cases of pernicious anaemia, leukaemia, bothriocephalus anaemia, and poisoning by nitrobenzol, saponin, &c. In secondary anaemias it does not occur, save in an attenuated form, associated with extreme reduction in the numbers of the red cells. A blood crisis of normoblastic type, on the other hand, is an indication of marrow activity, and may occur in many and varied conditions, and without extreme loss of the red cells. In the infant, however, a megaloblastic reaction has a somewhat different significance. Megalocytes, and even a few megaloblasts, may be found in the peripheral blood of the newly born, and a return to the foetal type of cell occurs in childhood under slighter provocation than in the adult, and in response to stimuli which are not necessarily specific. The degree of anaemia, too, is not infrequently quite out of proportion to its apparent cause.

Anaemia of severe degree associated with enlargement of the spleen is comparatively frequently met with in infants. It is most common in the second year of life, and may or may not be accompanied by rickets, though it seems certain that it has no causal connexion with that disease [17]. The liver is usually larger than normal, and the lymphatic glands may also be enlarged. There is little tendency to the occurrence of haemorrhage, but catarrhal complications are common. Recovery may occur, but in severe cases death as a rule ensues. 'The red corpuscles are always reduced in numbers, but rarely to an extreme degree . . . The haemoglobin is always reduced, but not necessarily in proportion to the reduction of red cells . . . The red corpuscles

[19] Dock, G., and Warthin, A. S., *Amer. Journ. Med. Sci.*, Phil., 1904, vol. cxxvii, p. 24.

are apt to vary a good deal in size, large forms being often met with . . . Nucleated corpuscles are usually present . . . the majority of them are normoblasts . . . but megaloblasts are also met with. A leucocytosis is usually present in these cases, but not invariably'; and, as Dr. Hutchison[20] points out, the tendency is to overestimate it, forgetting that the leucocyte count in infants between twelve and eighteen months of age averages 12,000–14,000 per c.mm. In certain cases, too, the leucocytosis is the result of some complication, often of a catarrhal nature. 'More usually the increase is chiefly to be ascribed to an augmented number of non-granular cells . . . [it] tends particularly to affect the larger lymphocytes and the large mononuclears, but every intermediate grade between these and the ordinary small lymphocyte is met with . . . There is, in fact, a marked polymorphism in these cases . . . Myelocytes are usually present . . .'

My own observations agree with Dr. Hutchison's summary.

This description of the blood in cases of splenic anaemia of infancy is almost identical with that of my cases described above. The main difference is the absence of leucocytosis, but its occurrence in infantile cases is not invariable. Six of Hutchison's cases showed leucocyte counts that were not excessive, two of Koplik's[21] cases, and four of my own (unpublished), in all twelve cases out of forty (30%).

In both of my cases ill-health was present at an early age. In one the spleen was known to be enlarged at the age of 9; in the other the child was 'anaemic' at the age of 4½. And the defective development of both patients is presumptive evidence in the same direction.

I have no new facts to bring forward with regard to the pathology of splenic anaemia occurring in adult life or in infancy. I simply wish to draw attention to the resemblance between my cases and those of splenic anaemia in infancy. Similar cases, too, have been recorded, though deficiencies in the details of the blood examinations make the resemblance less apparent. Dr. Hutchison states that there is a tendency for splenic anaemia in infancy to occur in more than one member of a family, a point on which I have no personal information; but the 'family' cases of splenic anaemia recorded by Collier, Springthorpe and Stirling, Bovaird, Wilson and Brill are examples of this tendency; and in several of these cases symptoms dated back even earlier than in my own.

Osler defines anaemia splenica chronica as 'a chronic affection, probably an intoxication of unknown origin', but at the present time we do not know whether the poison is specific or not. A similar uncertainty exists with regard to the splenic anaemia of infancy, though it is much less rare than the adult form. If they are specific, they may be separate and distinct from the etiological

[20] Hutchison, R., *Lancet*, London, 1904, vol. i, pp. 1253, 1323, 1402.
[21] Koplik, H., *Arch. of Ped.*, N. Y., 1907, vol. xxiv, p. 161.

point of view, or merely the same disease, modified by its occurrence at different periods of development.

The poison is almost certainly of portal origin. Abdominal symptoms had been severe at times in both of my cases, though the evidence of their character was somewhat indefinite; and in both, although gastro-intestinal symptoms were absent at the time of observation, oral sepsis was well marked.

I have great pleasure in acknowledging my indebtedness to Professor Gemmell for permission to make use of his clinical records in the Western Infirmary and the Royal Hospital for Sick Children.

BLOOD COUNTS IN SPLENIC ANAEMIA

Author		Age	Red Cells	Haemoglobin	Colour Index	Erythroblasts	White Cells	Polymorph			Myelocytes	Small lymphocytes	Large lymphocytes	Large mononuclears	Transitional	
								Neutrophil	Eosinophil	Basophil						
Osler	4	33	3,000,000	25	·41	...	2,800	84·4	2·8	...	...	4·4	...	5	3·4	Four months after haemorrhage
	5	38	4,000,000	30	·37	...	6,500	73	2	...	...	10	...	12	3·	
	7	40	4,816,000	55	·57	No N.R.'s	5,000	...	...	...	...	...	...	...	...	Large mononuclears more numerous than the small
	8	56	3,600,000	60	·75	No N.R.'s	3,000	66	1	...	...	25	...	7	2	
	9	58	4,788,000	60	·74	No N.R.'s	5,200	40	1·2	...	...	52	...	2	4·8	Slight increase in average size of red cells. A few microcytes and macrocytes
	10	39	4,128,000	45	·54	No N.R.'s	2,800	...	...	...	...	...	...	...	...	A few megalocytes and microcytes
	11	57	3,328,000	40	·60	An occasional N.R.	2-4,000	78	·5	...	...	6	...	13	2·5	
	12	40	4,208,000	45	·53	No N.R.'s	4,000	65·6	3·3	...	None	15	...	12·6	3·3	
	14	35	3,856,000	55	·72	No N.R.'s	4,500	73·7	1	...	None	14	...	8	3·3	
	15	43	4,270,000	45	·53	...	2,500	80·3	5	6	...	8	...	4	2	
	16	30	3,300,000	30	·45	No N.R.'s	2,400	...	...	...	...	...	...	...	...	
	17	40	2,500,000	47	·85	Two N.R.'s	2,500	67	2·6	...	...	21	...	5	1·9	August, 1898
			3,800,000	65	·77	...	2,000	...	...	...	...	...	...	...	...	August, 1900
			3,800,000	58	·68	...	4,200	80·6	1·2	...	...	9	...	5·8	3·4	Autumn, 1901
	18	33	3,026,000	53	·88	No N.R.'s	6,875	55·96	·37	·37	...	11·19	...	29·85	2·23	No macrocytes
Springthorpe and *Stirling*	1	28	2,960,000	65	1·00	...	8,000	...	...	...	None	...	...	...	...	No marked megalocytosis
(sister)	2	19	2,960,000	67·5	1·00	Some normoblasts	Leucopenia	...	...	...	...	...	...	...	...	
(sister)	3	23	...	...	...	...	...	...	...	...	...	...	...	...	...	
(brother)	4	30	2,250,000	65	1·4	Some N.R.'s	9,000	...	...	...	...	...	...	...	...	Many red cells larger than normal
(son of 4)	5	7	3,600,000	40	·55	Fairly abundant N.R.'s	14,100	...	...	...	...	...	...	...	...	Many megalocytes

(niece of 1)	6	10	2,564,000	55	·9	Numerous N.R.'s	11,860	...	...	...	...	In-creased	...	...	...	Many megalocytes
Summons		14	3,200,000	40	·6	No N.R.'s	9,380	...	...	...	...	...	...	...	...	Many megalocytes
Bovaird	1	3	4,440,000	75	·75	...	9,000	...	...	...	...	...	...	...	...	
		at age of 6	4,180,000	62	·67	...	14,000	57·5	1	...	...	12·5	...	29	...	
	2	13	2,880,000	60	·9	...	4,000	...	...	...	...	...	...	...	...	
		at age of 16	3,550,000	...	...	...	7,000	62	1·4	...	...	21	...	15	...	
Levison		27	2,537,000	22	·44	One megalo-blast	4,200	86·8	·75	...	None	6·06	...	6·31	...	A few megalocytes
Hammill		6	3,365,000	40	...	...	5,200	50·4	6	...	...	42	...	6	...	
		at age of 10	4,400,000	58	·66	...	3,680	82	3·4	...	...	8·6	...	1	5	Red cells normal
Bramwell		27	4,030,000	48	·6	No N.R.'s	3,800	84	1·6	1	None	9·3	3·3	...	...	
Williamson	1	9	3,030,000	22	·36	...	4,000	...	...	...	None	Increased		...	...	
	2	21	3,270,000	20	·33	...	Not increased	...	...	...	...	...	...	...	...	
Brill	1	9	No de	tails.	Died	at 9 years	of age with	en-	larged	sple	en.					
(sister)	2	30	3,800,000	65	·77	No N.R.'s	6,400	65	Few	...	...	30	...	5	...	
		34	4,200,000	70	·76	No N.R.'s	7,168	56	·75	...	...	35	...	8	...	
(brother)	3	23	5,400,000	90	·8	...	7,168	...	...	...	...	...	...	...	...	
		30	3,800,000	55	·72	No N.R.'s	5,120	54	·25	...	...	36	...	10	...	
Sippy		45	1,740,000	30	·86	No N.R.'s	5,214	66·4	·8	...	...	25	...	4	3	
Michell Clarke		19	1,171,000	12	·46	...	7,453	...	...	...	...	...	...	...	...	After severe haematemesis
			1,320,000	14	·48	A few normoblasts	5,250	58	3	(one)	(one)	28	...	11	...	
Scott	1	30	2,440,000	60	1·2	Numerous normoblasts; one megalo-blast	9,050	54·4	4·4	...	...	36	...	1·6	3·6	
	2	13	3,120,000	55	·79	...	3,600	58·4	2	...	...	26·8	...	6·8	6	
Dock and *Warthin*		41	3,640,000	60	·83	Some normoblasts	2,037	60·1	5	[7·3	'degen-erate' cells]	22·5	...	3·6	1·5	No megalocytes or myelocytes

N.R. = nucleated red cell.

'FAMILY' CASES OF SPLENIC ENLARGEMENT

Dr. Wm. Collier's Cases.

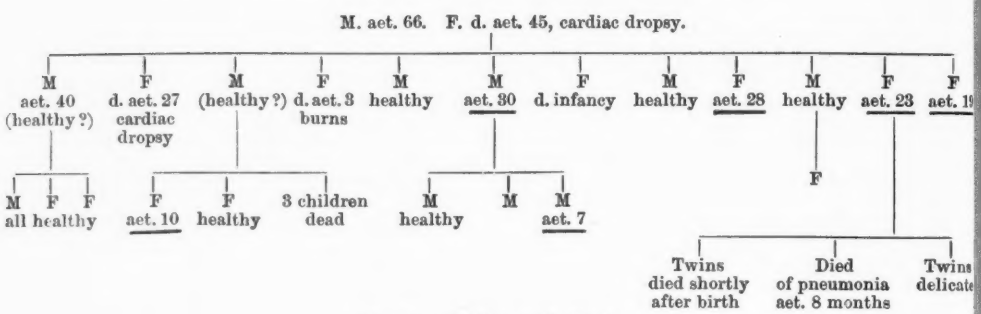
Seven children, of whom five are dead.

One died from inflammation of the lungs, two from tuberculosis of the bowel.

One died aet. six; marasmus; broncho-pneumonia and pleurisy; enlarged spleen (4 lb. 2 oz.). (Case reported.)

One died from bronchitis with an enlarged spleen (25 oz.).

Dr. J. W. Springthorpe and Dr. R. A. Stirling's Cases.



Cases reported are underlined.

Dr. D. Bovaird's Cases.

Father, mother, alive and well. Ten children.

One stillborn at 8 months.

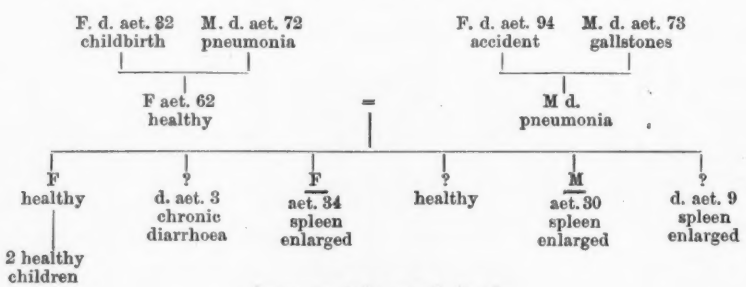
Four died during infancy from 'summer complaint'.

Three alive and well, aged 11, 8, 5.

One, aged 6, spleen greatly enlarged; liver somewhat large. (Case reported.)

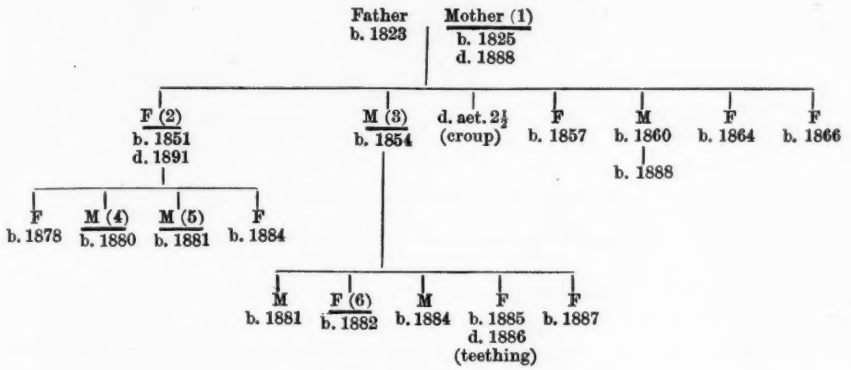
One, aged 16, spleen greatly enlarged; splenectomy; death. (Case reported.)

Dr. N. E. Brill's Cases.


F. d. aet. 82 childbirth
M. d. aet. 72 pneumonia
F. d. aet. 94 accident
M. d. aet. 73 gallstones
F aet. 62 healthy
=
M d. pneumonia
F healthy
2 healthy children
? d. aet. 3 chronic diarrhoea
F aet. 34 spleen enlarged
? healthy
M aet. 30 spleen enlarged
? d. aet. 9 spleen enlarged

Cases reported are underlined.

Dr. Claude Wilson's Cases.



Cases reported are underlined.

(1) Spleen enlarged about 1858.
(2) " " " 1858.
(3) " " " 1858.
(4) Spleen enlarged in 1889.
(5) " " " 1889.
(6) " " " 1889.

ON THE EXCRETION OF LEUCIN AND TYROSIN IN TWO CASES OF CARDIAC LIVER

By J. DIXON MANN, M.D., F.R.C.P.
Physician to the Salford Royal Hospital

In acute yellow atrophy of the liver, the appearance of leucin and tyrosin in the urine has long been recognized as an important indication, and very exceptionally these substances have been found in one or two other disorders of the liver; to these rare cases, the two which follow must be added.

Case I. A young man aged 20, suffering from advanced heart disease, was admitted into the Salford Royal Hospital in March, 1907. He was deeply cyanosed and was universally oedematous. The liver was not enlarged. On the sixth day after admission he became jaundiced. There was no elevation of temperature, nor any haemorrhage except that which was caused by a pulmonary infarct. The patient gradually sank and died on the tenth day after the appearance of the jaundice. Examination of the urine after the appearance of the jaundice gave the following results. It was scanty; dark in colour; acid in reaction; S. G. 1,023. It contained much bile-pigment. A faint trace of albumin was present, but no albumose, nor sugar. Microscopic examination showed the presence of octahedral crystals of calcium oxalate, and crystals of uric acid in the tablet form. About 300 c.c. of the urine were evaporated on the water-bath to a syrup and then left to crystallize. When examined with the microscope, crystals obviously of leucin and tyrosin were seen. Although the microscopic appearances were quite characteristic, corroboration by chemical tests was needed. Other specimens of the urine were precipitated with basic lead acetate and the filtrate, after being freed from lead by saturation with sulphuretted hydrogen, was evaporated to a syrup. After cooling, this was repeatedly extracted with small quantities of absolute alcohol in order to remove the urea, and finally was extracted with hot dilute alcohol and ammonia. After filtration, the extract was reduced to a small volume and was left to crystallize. The leucin and tyrosin were subsequently separated and were severally tested. The presence of leucin was demonstrated by Scherer's and by Hofmeister's tests, and by its solubilities; that of tyrosin by Piria's, and by Denigès's tests, and by its reaction with Millon's reagent. The averages of the nitrogen-excretion were as follows: urea-N = 73 per cent.; ammonia-N = 9·7 per cent.; extractive-N = 12·8 per cent.

Post-mortem examination.—The liver weighed three pounds four ounces. It was passively congested; it was bile-stained, and showed fatty changes. The

bile-ducts were patent, and the gall-bladder contained a small quantity of bile. Microscopic examination showed dilatation of the capillaries throughout the lobules, and extensive atrophy of the liver-cells. The fatty changes were most marked in the centre of the lobules. Many of the liver-cells contained bile. The condition of the organ corresponded to the contracting stage of an enlarged liver due to chronic heart disease.

Portions of the liver-substance were examined chemically for leucin and tyrosin, which were present in very small amounts.

Case II. A boy aged 14, with heart disease of several years' standing, was admitted in April, 1907. He was universally oedematous, and was deeply cyanosed; he seemed to be almost moribund. The liver was very large: it extended transversely across the abdomen below the umbilicus. There was no jaundice. Two specimens of the urine, voided on the first and the second days after admission, were dealt with as previously described, and were found to contain small amounts of leucin and tyrosin; examination of subsequent specimens gave negative results. In a few days the boy began to improve, and the liver to recede; the improvement continued until the heart became fully compensated, when he left the hospital for a convalescent home on June 20, 1907. The liver could then be barely felt below the costal margin. The patient had a good appetite and pronounced himself to be quite well.

Among the few diseases of the liver in which leucin and tyrosin have been found in the urine acute yellow atrophy stands at the head. Much less frequently have they been found in cases of acute phosphorus poisoning. Beale [1] found leucin in a case of 'chronic wasting of the liver', accompanied by jaundice. Tyson [2] found leucin in a case of 'atrophic disease of the liver' which continued almost a year before it terminated fatally. Ruge [3] found tyrosin, but not leucin, in the urine from a case of primary carcinoma of the liver. Langstein [4] also found tyrosin, but not leucin, in the urine of a woman who had jaundice with calculi in the common duct. Bonanni [5] found leucin and tyrosin in icterus gravis. Greco [6] found leucin in the urine from a case of advanced cirrhosis of the liver, the patient at the time being in a state of coma. Calabrese [7] also found leucin and tyrosin in advanced cirrhosis. Both leucin and tyrosin have been found in the urine in a few general diseases such as pernicious anaemia, leucocythaemia, and in certain fevers. Some of the reported cases are founded solely on the results of microscopical examinations of the deposits; this mode of identification is unconvincing unless corroborated by chemical tests. In the course of a series of investigations on urines, which for various purposes were evaporated to a syrupy consistence, some specimens being derived from healthy persons, I have frequently seen under the microscope large, spineless crystals of ammonium urate, and also other bodies which, as regards size, contour, trans-

[1] *Kidney Diseases*, 1869, p. 278.
[2] *Amer. Journ. Med. Sc.*, 1872, vol. i, p. 65.
[3] *Charité-Annalen*, 1896, vol. xxi, p. 173.
[4] *Wiener klin. Wochenschr.*, 1903, vol. xvi, p. 787.
[5] *Bul. Accad. med. di Roma*, 1900.
[6] *Clin. Med. Ital.*, 1899, vol. xxxviii, p. 230.
[7] *Il Morgagni*, 1897, vol. xxxix, p. 513.

lucency, and colour, closely resembled leucin crystals. These bodies are unaccompanied by tyrosin, and as they are insoluble in dilute alcohol and ammonia they are not met with in the final extract made according to the method of isolation previously described. This want of solubility is a safeguard against error: any fictitious crystals are arrested by the filtration of the final extract and are to be found on the filter.

The presence of leucin and tyrosin in the urine from the cases I have described may be accounted for in one of two ways. (*a*) By autodigestion of the liver which along with other organs contains proteolytic ferments capable of inducing autolysis. One of the results of autolysis is the abundant production of amino acids which, when thus developed, are simply disintegration-products of the liver substance. It is assumed, and probably correctly, that autolysis can take place during life, but of this no direct proof is forthcoming. (*b*) Through defective cleavage of the amino acids which are produced in the course of the normal digestion of proteid in the small intestine. The extent of cleavage undergone by proteid during tryptic digestion is uncertain; but, whether the proteid molecule is entirely resolved into its primary constituents or not, leucin and tyrosin are split off from it; leucin being by far the most abundant of the cleavage-products. In their turn, and at an early period of their appearance, the amino acids are themselves subjected to cleavage by which they are disamidized: the amino group is split off with separation of ammonia, the carbon-containing moiety being oxidized. It is doubtful how far this power of cleavage of the amino acids extends: whether it is common to most organs, or is exclusively a function of the liver. Assuming that the liver is the chief, if not the only organ concerned, it is to be inferred that when the amino acids reach the liver in the normal condition, disamidization is effected by the intracellular ferments, and the ammonia that is detached is synthesised into urea. In this way leucin as the preponderating proteid-constituent contributes its quota towards the building up of urea. If the activity of the liver-cells be profoundly depressed, the intracellular ferments will be proportionately enfeebled; should the enfeeblement exceed certain limits, the ferments will be incapable of dealing with the whole of the leucin and tyrosin (together with other less easily recognizable amino acids) some of which will consequently pass unchanged into the urine. In relation to this it is interesting to note that leucin and tyrosin have been found in the urine in cases of cystinuria (Moreigne[8]; Abderhalden and Schittenhelm[9]). Since cystinuria is the result of an inherent anomaly of proteid-metabolism, it is to be inferred in these cases that the presence in the urine of leucin and tyrosin along with cystin simply indicates the existence of a more extensive derangement of proteid-metabolism than that which gives rise to the excretion of cystin alone.

At the present time, the occurrence of leucin and tyrosin in the urine is

[8] *Compt. rend. Soc. Biologie*, 1898, vol. l, p. 1097.
[9] *Zeitschr. f. physiol. Chem.*, 1905, vol. xlv, p. 468.

almost universally accounted for by the autolytic theory. There is, however, something to be said in favour of the older view that attributes the abnormality to faulty dealing on the part of the liver with some of the normal products of tryptic digestion. The results which obtained in the cases I have described seem to support the older view. In Case I, the daily output of leucin and tyrosin during the last ten days of life was considerably more than could have been derived from autolysis of the liver-tissue, seeing that after death the organ was of fair average weight—fifty-two ounces. The liver showed no indications of having undergone extensive autolysis; and when examined chemically it yielded but little leucin and tyrosin. Had the leucin and tyrosin which appeared in the urine been solely derived from autolysis of the liver, the amount of them obtained from it after death would have been immeasurably greater than it was. In experimental investigations on autolysis in animals, leucin and tyrosin have been found in the liver in greater amount, after death, than they appeared in the urine during life. Two factors are contributory to this: increased activity of autolysis after death, and the accumulation in the liver of the products then formed.

It is probable that the changes in the liver-cells vary in degree rather than in kind: from those which are so insignificant as to give rise to barely recognizable results, through all gradations, up to those which cause profound disturbances of metabolism, and are associated with the presence of intermediate products in the urine. It appears that severe derangement of the hepatic ferments may be evanescent. In my second case, forty-eight hours' rest and treatment rehabilitated the heart and restored the activity of the liver. In both these cases, there was profound cyanosis and great systemic disturbance at the time that leucin and tyrosin were excreted.

ADDITIONAL OBSERVATIONS ON MICROBIC CYANOSIS

By G. A. GIBSON, M.D.

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It is just five years since Stokvis[1] described for the first time the occurrence of cyanosis as the result of intestinal troubles. In his original case, he believed that the cyanotic appearance was produced by methaemoglobin, but no attempt was made to discover the manner in which the blood changes were produced. The patient had great intestinal irritation, clubbing of the fingers, deep cyanosis, and considerable albuminuria, and after death it was discovered that he had suffered from ulcerative enteritis with parenchymatous nephritis. Talma[2] placed on record three cases in which he concluded that methaemoglobin was present in the blood corpuscles but not free in the blood plasma. The renal secretion contained a large amount of indol, and in all these cases the condition of the intestinal tract was evidently the cause of the cyanosis. Hijmans van den Bergh[3] added largely to our knowledge of this interesting condition. He narrated the cases of three patients suffering from enterogenous methaemoglobinaemia, and found the connecting link between the intestinal troubles and the resulting blood changes to lie in the presence of nitrites. In connexion with this aspect of the subject, he applied the observations of Steensma[4] to his investigations. Besides these three cases of methaemoglobinaemia, he further described four cases of sulphaemoglobinaemia. Such was the state of our knowledge last year when a patient, who was brought to see me by Dr. W. F. Somerville, aroused in my mind the suspicion that such a condition was present. The patient was a married lady, aged thirty-six years, who had suffered for some years from weakness and headaches often associated with giddiness and faintness. The most obvious symptom was a profound change in the complexion: the patient had blue eyes and golden hair formerly associated with a ruddy complexion, but, during the last two or three years, the tint of the skin had become distinctly cyanotic. The face and hands were of a lavender hue, while the lips, ears, and nails were nearly as dark as bilberries. The blood showed considerable changes — estimation gave 48 per cent. of haemoglobin, and 3,200,000 erythrocytes, the colour index being therefore ·75; the leucocyte

[1] *Nederlandsch Tijdschrift voor Geneeskunde*, 1902, II. Deel, S. 678.

[2] Ibid. 1902, II. Deel, S. 721.

[3] *Deutsches Archiv für klinische Medicin*, 1905, S. 86, and *Berliner klinische Wochenschrift*, 1906, S. 7.

[4] *Nederlandsch Tijdschrift voor Geneeskunde*, 1904, II. Deel, S. 425.

[Q. J. M., Oct. 1907.]

count was 7,400. Stained films showed considerable poikilocytosis but no polychromatophilia, and no nucleated red corpuscles were to be seen. A differential count showed a percentage of 65 polynuclears, 28 small lymphocytes, 5 large lymphocytes, and 2 eosinophiles. There was great intestinal irritation accompanied by frequent gastric disturbances. The urine was free from albumin. In consequence of my suspicions as to the origin of the affection, it seemed to me advisable to have a thorough spectroscopic and bacteriological examination of the blood and the secretions. Dr. Somerville accordingly obtained the assistance of Dr. Carstairs Douglas with a view to a thorough investigation. The blood in dilute solution showed the characteristic spectrum of methaemoglobin, i.e., the narrow band in the red between the *C* and *D* lines, as well as the ordinary bands of oxyhaemoglobin in *D* and *E*. The urine contained nothing abnormal except a slight increase of urobilin determined by Schlesinger's test. Further investigations of the blood by Carstairs Douglas showed that it was extremely dark in colour and yielded a crimson solution when water was added to it, instead of the ordinary red colour. The spectrum of methaemoglobin was most distinct. With the delicate test, consisting in the employment of sulphanilic acid and naphthylamine in acetic acid, it was found that the blood contained nitrites in considerable amount. The saliva tested at the same time gave a distinct reaction for nitrites, very much more marked than in the case of some normal saliva used as a control observation. The faeces contained nitrites but no methaemoglobin, and fresh ox-blood mixed with a saline extract of the faeces gave negative results.

These facts indicated that methaemoglobin was present in the blood and absent from the faeces; that nitrites were freely present in the blood and saliva, but existed only in small amounts in the faeces, and that the latter possessed no power of converting normal ox-blood into methaemoglobin. They appeared to indicate a haematogenous formation of the nitrites, and raised the question whether the source of these bodies might not be bacterial. Two loopfuls of diluted blood were, therefore, inoculated into ordinary nutrient agar, which was plated and incubated at 37°C. for twenty-four hours. At the end of this time the plate showed a number of discrete bluish-white colonies, each from one to two millimetres in diameter. Inoculations of these into various culture media yielded the following results:—(1) agar slope: a thick, whitish-grey, moist streak; (2) broth: a general turbidity settling down to a whitish deposit; (3) potato: a slight brown growth; (4) glucose-agar: gas and acid production; (5) lactose-agar: gas production; (6) neutral-red-agar: development of fluorescence; (7) gelatin-stab: the tube medium unfortunately liquified entirely owing to the very warm weather; (8) milk: marked curdling; and (9) peptone water: indol reaction. Attention was then directed to the question whether the organism had produced nitrites as well as indol in peptone water, as the cholera vibrio does. The addition of sulphuric acid alone, however, gave rise to no formation of indol red, but the subsequent addition of a trace of nitrite of sodium permitted of the formation of

a red tint. Microscopically the organism was a short, stout rod, staining with the ordinary basic dyes; it was gram-negative. Motility in hanging-drop preparations was marked.

From these investigations it seemed clear that the organism was either the bacillus coli communis or some very closely allied organism of the colon group. It was apparently without the power of producing nitrites in peptone water, but it was impossible to say what the result of its chemical activity within the blood might be. Our provisional conclusions were that the original source of mischief was in the bowel and that a systemic infection had taken place, whereby nitrites were continuously produced in the body in varying amounts, (thus probably explaining the fluctuations in the cyanosis), and that the nitrites acting on the haemoglobin constantly altered a varying amount of it into methaemoglobin, a condition in which oxygen is very firmly united to the haemoglobin molecule and cannot be separated from it for the needs of the body cells. We pointed out, finally, that the condition was a member of the group of affections to which the term 'false cyanosis' is sometimes applied.

These observations were published by Carstairs Douglas and myself[5] in the course of last year. A few months afterwards West and Clarke[6] placed on record for the first time in this country an interesting observation on idiopathic sulphaemoglobinaemia closely resembling in its general features the cases described by Hijmans van den Bergh.

Dr. Somerville has recently been so kind as to afford me an opportunity of again seeing his patient, and as the result of very careful and assiduous intestinal antisepsis a great improvement had occurred. The patient was still somewhat pale, but there was scarcely a trace of cyanosis, while the headaches and other nervous symptoms had become less marked. The percentage of haemoglobin was 66, and the number of erythrocytes 3,600,000—the colour index was, therefore, ·92. The leucocytes amounted to 7,900. Stained films showed that both erythrocytes and leucocytes were fairly well formed and manifested normal staining. No poikilocytosis was present and no erythroblasts could be detected. A differential count of the leucocytes showed a normal proportion of the different varieties. Spectroscopic examination of the blood showed it to be practically normal, and no trace of methaemoglobin could be detected, the spectrum of oxyhaemoglobin alone was present, shown by the ordinary lines at *D* and *E*. The proteids were precipitated in absolute alcohol and allowed to settle. The clear fluid remaining was centrifugalized and gave a very delicate but still perceptible nitrite reaction. Blood taken under strict aseptic precautions from the ear was inoculated directly into agar, and also, after dilution with sterile water, plated on agar and on gelatin. No growth occurred at all in the agar, and in the gelatin only a mould, evidently from accidental contamination. Not a trace of any coliform organism could be detected. The result of treatment in this case seems to me to bear out

[5] *The Lancet*, 1906, vol. ii, p. 72.
[6] *The Lancet*, 1907, vol. i, p. 272.

the conclusions arrived at as the result of the spectroscopic and bacteriological investigations carried out for me last year by Carstairs Douglas. If absolute recovery does not take place by means of intestinal antisepsis, it will be our duty to recommend that the great intestine should be washed out by an opening into the caecum.

Toxic processes having their origin in local infection by means of the bacillus coli are now widely recognized, and various forms of general disturbances produced by enteric and vesical changes brought about by this organism have been carefully studied. That the organisms may enter the blood and produce such profound changes as we have described is an entirely new conception. The observations of Stokvis, Talma, and Hijmans van den Bergh have shown that methaemoglobin and sulphaemoglobin may be produced as the result of enteric changes. The presence of methaemoglobin in the blood has been confirmed in this country by Carstairs Douglas and myself, and that of sulphaemoglobin by West and Clarke. The existence of the bacillus coli in the blood had not been recorded before the publication of our observations. A careful review of the whole facts convinces me that in the condition which has been described we are dealing with a hitherto undescribed but perfectly definite form of disease.

It may be concluded that the bacillus coli may give rise to three stages of infection. There may, in the first place, be simple enteritis with diarrhoea, headaches, and depression, showing a tendency to develop ulceration and liable to cause fatal marasmus. This condition is often removed by intestinal antiseptics, but such methods occasionally fail entirely. Until quite recently this affection was frequently fatal, but it can now be removed by irrigation of the colon by means of an operation on the caecum. In the second place, a further development arises when, as the result of changes in the intestine similar to those just referred to there is a formation of nitrites which, being absorbed into the blood, give rise to methaemoglobin or sulphaemoglobin and resulting cyanosis. Such a condition is susceptible of improvement under antiseptic treatment, but a review of the cases published in the Netherlands is not calculated to arouse sanguine anticipations; for this also surgical measures should be very carefully considered. The entrance of the bacilli into the blood and their multiplication there, with which the present paper has dealt, seems, lastly, to be but a further development of the same process. As the subject has been fully considered in the preceding pages, it is unnecessary to add any further remarks.

ON SUPRARENAL SARCOMA IN CHILDREN WITH METASTASES IN THE SKULL

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With Plates 1–3

I wish to direct attention in this paper to what one may describe, for want of a better term, as a definite 'clinical syndrome', occasionally met with in children. I refer to cases of sarcoma of one or other suprarenal with metastases in the bones of the skull. In the accompanying table I have epitomized the notes of seven hitherto unpublished cases of this combination along with those of three others which are all that a fairly thorough search of medical literature has enabled me to discover.

All the patients are children, their ages varying from nine months to nearly nine years. Seven are boys, and three girls. In their clinical features the cases resemble one another very closely, and may be briefly outlined as follows :—

In the majority of the cases the first thing noticed was some swelling about the bones of the skull, which in several of them was ascribed to a fall or injury. Following, or sometimes preceding this, proptosis of one or both eyes was observed. In two-thirds of the cases discoloration of the eyelids on one or both sides is reported, and in a few instances this was the first point to attract attention. Anaemia is a striking feature in all the cases, the blood changes being those of a profound secondary anaemia. Leucocytosis has not been recorded in any case. An abdominal tumour in one or other loin was felt in only five of the cases. The progress of the disease in every instance has been rapid, and the younger the patient the more rapid it appears to have been. Thus the duration of life from the time the earliest signs were observed was, in the oldest child, about six months, and in the youngest of the series only one month. The advance of the growth is marked by progressive exhaustion and anaemia, by indications of increased intracranial pressure such as torpor, intense optic neuritis[1] and blindness. The tumours on the head

[1] Mr. J. Herbert Parsons has kindly furnished me with the following note on the condition of the fundus in one of these cases (No. 4 in the Table) :—

The Eyes. Apart from the proptosis of the right eye due to the orbital growth the fundi

increase in size, often filling up the temporal fossae, and the proptosis becomes excessive, the cornea in some cases becoming ulcerated and destroyed, and the lens escaping from the globe. The accompanying photographs show the characteristic appearances better than any verbal description.

The post-mortem features are also very constant. In all there was found a sarcoma of the suprarenal, usually consisting of small round cells, situated on the left side in six, and on the right side in four of the cases. The most extensive metastases were found in the bones of the vault and base of the skull, producing the swellings on the head and protrusion of the eyes observed during life. The striking appearance presented by the interior of the calvarium in one of my cases is shown in Plate 3, *b*, the same was found in a greater or less degree in all the others I have seen. Metastases are also met with in the ribs, sternum, and vertebrae, but not, apparently (except in Case 1) in the long bones, though these may not always have been carefully examined. Secondary deposits in the internal organs appear to be exceptional. The adjoining kidney has sometimes been involved, but rather, it would seem, by direct extension of the growth than by true secondary deposits. The liver may become similarly invaded when the tumour starts in the right suprarenal, but in one case (No. V), it was the seat of a small secondary nodule when the primary growth was on the left side. As a rule, however, the viscera are spared.

The diagnosis of these cases during life presents little difficulty if only one's attention has once been directed to them. The important point to bear in mind is that the most striking signs, and those which first advertise the case, are those which are produced by the secondary deposits in the skull. The primary growth may, indeed, be entirely overlooked, and in some of the cases

showed intense optic neuritis of the 'choked disk' type. The disks were swollen to about 6 D; there was a large amount of white exudate, but no haemorrhages. The veins were dilated and very tortuous; in places they were hidden by exudate. The arteries curved over the swollen disk, and were also hidden in places by exudate. The retina immediately surrounding the disk was oedematous, the whitish area fading off into normal retina at about one disk's breadth from the disk. The periphery of the retina was normal. The macula of the right eye showed an imperfect macular 'star', such as is frequently characteristic of albuminuric retinitis; the star was perfect above, but absent below. The left macula showed a similar though more pronounced condition. Here there were large spots of glistening white material, the largest being in the centre of the macula; the smaller surrounding spots, all strictly limited to the macular region, showed a somewhat radial arrangement.

The picture therefore resembles that commonly regarded as characteristic of albuminuric retinitis in the presence of papillitis and macular stars; it differs from this condition in the choked disk nature of the papillitis, the swelling being greater than is usually observed in cases of renal neuro-retinitis.

I regard the condition as due entirely to increased intracranial pressure, a view which is supported by the absence of albumin in the urine. In my experience the presence of the macular star in these cases, which is very rare in adults, is very common in children with increased intracranial pressure. I am inclined to think that it is more frequently present than absent in children. Possibly the frequency of hypermetropia in children may account for this fact, the posterior pole of the eye having not yet assumed its final position. The retina is thus more readily rucked up in this situation by oedema. The tortuosity of the vessels in hypermetropic eyes may be adduced as supporting this opinion.

it could not be detected even although the suprarenal regions were specially examined for it by palpation. Nevertheless, one can safely predict that a suprarenal tumour will probably be found after death.

There are two diseases which tend to simulate the appearance presented by such cases. Infantile scurvy may produce very similar ecchymosis of the eyelids, and chloroma may cause identical proptosis and tumours about the skull. Scurvy can be excluded by the absence of other signs, and the failure of antiscorbutic remedies; chloroma by the absence of a lymphocytosis.

As regards the pathology of the cases here described, I am not in a position to express a confident opinion, as it is many years since some of them were recorded, and our whole conception of the nature of malignant tumours of the suprarenal has been changed in quite recent times. They are all described in the records as cases of 'sarcoma', and usually of the small round-celled variety, but it is quite possible that some of them at least may really have belonged to the group of tumours now commonly spoken of as 'malignant hypernephromata', which are more of the carcinomatous type. Thus, in Case IV there was certainly some doubt whether the tumour should be classed as a sarcoma or as a 'papilloma'. The report of the pathologist (Dr. C. H. Miller) on Case VI was as follows:—

The section of the primary tumour shows the following structures:—

1. A thick, fibrous capsule.
2. Coarse trabeculae arising from this capsule; some of these were definitely fibrous, others were undergoing hyaline degeneration. Many were invaded by small round cells.
3. The tumour cells, which were arranged in solid clumps between the trabeculae.
   These cells were round, oval, and a few were spindle-shaped.
   The oval cells were the largest, and their protoplasm was granular.
   The round cells were very numerous, and stained darkly; their nuclei occupied a relatively large space. The spindle cells were fine and delicate. Their fine terminal processes served to form a very delicate stroma, which was in no way connected with the coarse trabeculae.
4. Red blood corpuscles in quantities. Some were amongst the tumour cells, some in the trabeculae. Many were in spaces which were not lined by endothelium. There were signs of blood vessels.

Under a low power there was a general resemblance to the suprarenal cortex.

The secondary growth closely resembled the primary, but the central parts of the larger masses were necrotic.

On the other hand I have recently re-examined sections from the tumour in Case X, which had been preserved in the London Hospital Museum, and it certainly presented the characters of a sarcoma, and not those of a malignant hypernephroma.

Cases of malignant hypernephroma with metastases in the bones have quite recently been published by Scudder.[2] He was able to collect seventeen

[2] *Publications of the Massachusetts General Hospital*, Boston, vol. i, No. 3, p. 82, June 1907.

cases, all in adults, but in the majority of these the secondary deposits were in the long bones, and only in four did they occur in the skull. In his cases the tumours were of the carcinomatous type, and in many of them the course was slow, but they resemble the cases described above, in that the bone metastases were often the first indication of the disease. Why malignant tumours of the suprarenal tumours tend to have their metastases mainly, and sometimes exclusively, in the bones it is impossible to say. It is noteworthy that in none of my cases was there any indication of premature sexual development such as has been described as a consequence of malignant hypernephromata in childhood by Bulloch and Sequeira,[3] which is in harmony with their conclusion that 'cases of primary blastomata of the suprarenal glands and unassociated with precocity are usually lympho-sarcomata'.

SUMMARY OF CASES OF SUPRARENAL TUMOUR WITH METASTASES IN THE SKULL.

SEX	AGE	HISTORY AND SYMPTOMS	BLOOD	RESULT OF POST-MORTEM
1[4]. Boy .	$8\frac{9}{12}$ years	Headache and vomiting since a blow on forehead five months before admission. Ecchymosis left eye since injury. Left cervical glands enlarged. Tumour in left loin. Left eye became proptosed and cornea finally destroyed. Tumour on upper third of left tibia. Death in six months from onset	Not recorded . .	Large tumour in left side of abdomen involving left kidney and suprarenal; calvarium infiltrated with growth. No secondary deposits elsewhere
2[4]. Boy .	10 months	Swellings on head first noticed. Left eye proptosed. Haemorrhage into orbit. (Plate 2, *c*.) Supposed at first to be scurvy. Died soon after admission	Reds, 3,125,000; Whites, 12,000. No abnormal white cells	Small round-celled sarcoma of medullary part of left suprarenal; calvarium and cervical glands infiltrated. No secondary deposits elsewhere
3[4]. Boy .	$2\frac{1}{2}$ years .	Lumps on head noticed five months before admission. Tumours of forehead and temporal fossae, ecchymosis and proptosis of right eyeball. Liver enlarged (3 f. b.) Profound anaemia. Died six weeks after admission	Profound secondary anaemia Reds, 1,572,000; Hb. 45 per cent.; Whites, 14,500; Polynuclears, 31 per cent.	Right suprarenal contained tumour size of a walnut. (Round- and oval-celled sarcoma.) Secondary nodules in liver and cervical glands. Extensive growths in calvarium and base of skull

[3] *Transactions of the Pathological Society of London*, vol. lvi, 1905, p. 189.

[4] Cases 1, 2, 3, and 4 are derived from the Records of the Hospital for Sick Children, Great Ormond Street. Cases 5, 6, and 10 from those of the London Hospital.

Sex	Age	History and Symptoms	Blood	Result of Post-mortem
4[4]. Girl .	4 years .	Pains in limbs and head for six months. Great weakness. Tumour in left hypochondrium. After admission developed optic neuritis, lumps in forehead and proptosis (L). Died three and a half months after admission	Reds, 3,942,000; Whites, 10,500; Polynuclears, 51 per cent.; Hb. 70 per cent.	Large nodular growth in position of left suprarenal capsule, a small remnant of which could still be recognized adherent to it. Deposits in lymphatic glands all over the body, in the bones of the skull, and on the inner aspects of all the ribs except the first. No metastases in the viscera. The growth consisted of round and oval cells (?Sarcoma; ?Papilloma)
5[5]. Boy .	2½ years .	Fall on head three weeks before admission. Swelling of eyes and face started afterwards. Both eyes now proptosed. Ecchymosis of lids. Growths in temporal fossae and swelling felt in left hypochondrium	Reds, 3,200,000; Whites, 8,400; Polynuclears, 47 per cent.	Sarcoma of left suprarenal. Infiltration of calvarium with new growth. Small nodule in liver
6. Boy .	3 years .	Ill two weeks, but getting pale for considerable time. Profoundly anaemic. Haemorrhage from gums. Growth appeared in left temporal fossa. Slight proptosis of left eye. Optic neuritis. Blindness. No tumour felt in abdomen. Urine normal. Died nine weeks after onset	Severe secondary anaemia. No leucocytosis. Reds; 1,400,000; Hb. 35 per cent.; Whites, 8,000; Polynuclears, 65 per cent.	Sarcoma of medullary part of left suprarenal. Infiltration of calvarium (Pl. 3, *b*) and thoracic spinal column. Growth showed round, oval and a few spindle cells arranged in clumps separated by trabeculae
7[6]. Boy .	5 years .	Slight fall six weeks before admission: three weeks later severe pain in back; one week later discoloration of eyelids. Gradual wasting: no vomiting. Marked double proptosis with discoloration of lids; waxy pallor. Swellings on head. Large tumour in right flank. Liver down to umbilicus. Glands in neck palpable. Optic neuritis. Progressive asthenia and anaemia. Rupture of cornea. Death three weeks after admission	Reds, 2,050,000; Hb. 50 per cent.; Whites, 10,000; Polynuclears, 41 per cent.	Large mass of retroperitoneal new growth (small round-celled sarcoma), involving and surrounding right kidney, and invading liver. Extensive secondary deposits in vault and base of skull: also in sternum; other organs unaffected. Bones of spine and limbs not examined

[5] A brief report of this case has already been given by Barnard. *Clin. Soc. Trans.*, vol. xxxvii, 1904, p. 216.

[6] Ogden and Mathews, *Brit. Journ. of Children's Diseases*, vol. iii, 1906, p. 394.

Sex	Age	History and Symptoms	Blood	Result of Post-mortem
8[7]. Girl .	9 months	Brought for swelling of the temple and protrusion of right eye-ball. Tumour felt in right loin. Growths appeared on skull. Death in five weeks	Not reported . .	Medullary sarcoma of right suprarenal. Secondary deposits in ribs, skull, kidneys, and left ovary
9[8]. Girl .	$1\frac{2}{12}$ years	Two weeks before admission developed swelling of abdomen, followed by discoloration of right upper eyelid. Very pale; right lid ecchymosed. Palpable tumour in right loin. Operation. Death	Not reported . .	Small round-celled sarcoma (? congenital) of right suprarenal, liver and pancreas. Metastases in mesenteric and retro-peritoneal glands and in bones of skull.
10. Boy .	3 years .	Admitted with double proptosis. Both upper lids blackish (? haemorrhagic). Haemorrhage into left conjunctiva. Ovoid elastic tumour over right parietal eminence. Rounded prominence just above right ear (? haematoma). Profoundly anaemic. Spleen palpable. Urine normal. Blackening of left eye noticed four weeks before admission. No history of injury. As the case progressed the abdomen became tender, but no definite tumour was felt. The child died four weeks after admission	Not recorded . .	Large mass above left kidney which was easily separated from surrounding tissues. Neighbouring glands enlarged by infiltration of the growth: no evidence of a suprarenal capsule. On section the mass was solid and somewhat resembled a large gumma. Entire surface of skull covered by huge masses of new growth, which was for the most part soft on section but contained some spicules of bone. The growth invaded both orbits, but not the cavernous sinuses. No enlargement of mediastinal glands. No deposits elsewhere. Microscopical examination showed a lympho-sarcoma

[7] Cohn, *Berlin. Klin. Wochensch.*, xxxi, 1894, p. 266.

[8] Bruck, *Jahrb. f. Kinderheilk.*, vol. lxii, 1905, p. 82.

(a)

(b)

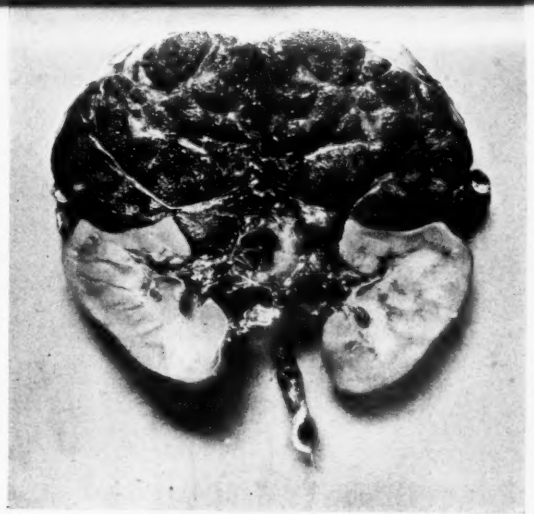
(c)

(d)

(e)

a, *b* and *c*, various stages of the disease in Case IV; *d* and *e*, tumour from Case IV.

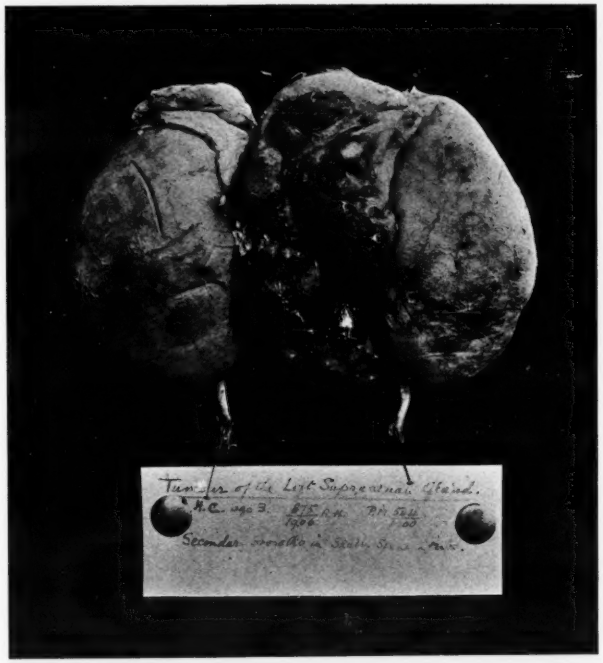
(*a*)



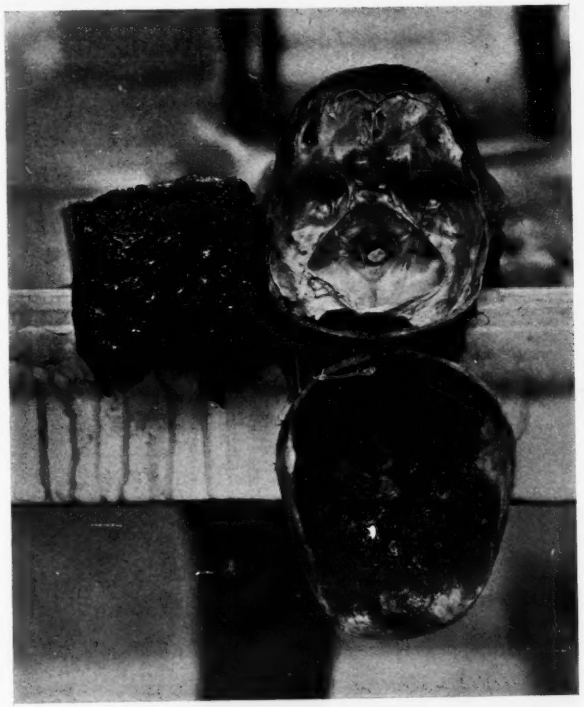
(*b*)

(*c*)

a, Case VI; *b*, tumour from Case II; *c*, Case II.



(*a*)



(*b*)

a, the kidneys and supra renals; (*b*) the interior of the skull in Case VI.

ABNORMAL INCEPTION OF THE CARDIAC RHYTHM

By JAMES MACKENZIE, M.D., Burnley

With Plates 4–9

It is my desire to direct attention to what may be considered a new conception of the cause of a very common form of heart failure, and to show that the principles underlying this new conception are not only of the greatest clinical significance, but are of the highest importance in affording a key to the pathology of the irregular heart.

The class of cases.—The class of cases to which I refer are those in whom a very prominent and easily recognized symptom is a continuous irregularity of the heart's action. These cases are found under two conditions, first, in the later stages of mitral disease, especially of mitral stenosis, and, second, in those cases of irregular heart action so common in advancing years, and usually associated with arterio-sclerosis. Of the comparative frequency of these cases I find that more than one half of the patients with serious heart failure that I am called upon to treat belong to this category. The basis of this paper rests upon careful observations of more than six hundred patients, many of whom I have watched from five to twenty years.

The argument.—The proposition I wish to present is that in these cases the normal sequence of the heart's contraction no longer prevails, that the ventricles alone may contract, or that the auricles and the ventricles contract simultaneously. As a deduction from the facts proving the foregoing proposition, I suggest that the stimulus for contraction arises no longer from the normal place at the mouths of the great veins, e.g. from the sinus node which Keith and Flack[1] have found at the root of the superior vena cava, the point that is probably the starting-point of the heart's contraction; but at the *a–v* node (Knoten) described by Aschoff and Tawara[2] situated at the auriculo-ventricular junction.

The nature of the clinical evidence.—The evidence I bring in support of this suggestion is mainly a logical inference from certain clinical facts supported by the results of Dr. Keith's examination of a number of hearts from which I had obtained during life my clinical data, and from certain experimental results. The clinical evidence consists, first, in the demonstration that when

[1] Keith, A. and Flack, M., 'The form and nature of the Muscular Connexions between the Primary Divisions of the Vertebrate Heart.' *Journal of Anatomy and Physiology*, vol. xli, 1907, p. 172.

[2] Tawara, S., *Das Reizleitungssystem des Säugetierherzens* Gustav Fischer, Jena, 1906.

the heart takes on this irregular action all the signs of auricular systole that had been previously present at once disappear. The deduction is that when this happens the auricular systole no longer occupies its normal place in the cardiac cycle. Second, in the demonstration of the fact that the auricle contracts at the same time as the ventricle.

The nature of the irregularity.—Before proceeding to the demonstration of these facts I may point out the peculiar features of the irregularity in question. In a great majority of irregularities, apart from those we are now considering, there is a certain order in their appearance; the irregularity varies, for instance, with the respiration, or the fundamental rhythm of the heart is unchanged, but is interrupted by the premature occurrence of an occasional contraction of the auricle or ventricle (Fig. 14), or the disappearance of an occasional ventricular contraction. In the irregularities of which I speak there is no order: short and long cardiac cycles appear in the most disorderly fashion. At times a seeming orderliness may appear, but if analysed it will be found that the cardiac cycle is continuously varying, and hence I refer to this form of irregularity as a 'disorderly rhythm' (see Fig. 1). A slower rate with this irregularity is seen in Figs. 3, 4, 10, &c.

An exception to this statement should be made in regard to those cases where, though the starting-point is the same, the heart contracts with great rapidity and regularity, as in certain forms of paroxysmal tachycardia.

The evidence of auricular contraction.—The first series of facts that I shall produce to show the real meaning of the changes in the heart demonstrate the disappearance of all signs of auricular contraction at the normal period of the cardiac cycle. The clinical evidence of auricular systole found more or less frequently are:—

(1) A wave in the jugular pulse-tracing due to a contraction of the right auricle.

(2) A wave in the apex tracing due to a contraction of the left auricle.

(3) A wave in the liver pulse due to a contraction of the right auricle.

(4) A presystolic mitral murmur due to a contraction of the left auricle.

(5) A presystolic tricuspid murmur due to a contraction of the right auricle.

If we take first the evidence in the jugular pulse we find normally a wave preceding the carotid and radial pulse as in Fig. 2, where the wave, *a*, from its position in the cardiac cycle, is recognized as being due to the auricular systole. When the irregularity of which I speak arises, the character of the venous pulse at once changes, and we get a form of venous pulse in which there is no evidence of an auricular contraction in the normal period; in other words, the jugular pulse changes from one of the auricular type to one of the ventricular type (Fig. 3). If there should have been present a presystolic murmur of the crescendo type it at once disappears, though a low-toned diastolic murmur may remain.

ILLUSTRATIVE CASES WITH MITRAL AND TRICUSPID DISEASE.

Case I. The first case I cite illustrates this change, where the disappearance of the auricular wave from the venous pulse, and the disappearance of the presystolic mitral murmur occurred simultaneously with a continuous irregularity. I first saw this patient in 1895, she being then thirty-one years of age. There was a history of acute rheumatism, and she had marked mitral stenosis. She became pregnant in 1896, and I watched her during the pregnancy and puerperium. She had a long illness from gastric ulcer in 1899. During these years I made frequent observations on her heart. It was invariably regular, and the jugular pulse always showed a well-marked wave due to the systole of the right auricle. There was at first a presystolic mitral murmur of the crescendo type, and latterly a long murmur following the second sound and running up to the crescendo presystolic murmur. The position of the presystolic murmur in the cardiac cycle is diagrammatically represented in the shading under the radial tracing in Fig. 2. This perfect regularity of the heart's action continued until she suffered from an attack of heart failure in 1900. Coincident with this failure the heart's action became irregular, and the jugular pulse showed no sign of a wave due to the auricular systole at the normal period of the cardiac cycle (Fig. 3). The crescendo presystolic murmur had disappeared while the diastolic portion persisted, as shown by the shading under the radial tracing in Fig. 4.

From this date until she died in 1907 these altered conditions persisted, Fig. 4 being a simultaneous tracing of the jugular pulse and radial taken in December, 1906.

Concerning the jugular pulse, it will be seen that in neither Figs. 3, 4, nor 5 at the normal period in the cardiac cycle is there the slightest sign of the auricular wave, *a*, which is so marked a feature in Fig. 2. At times the rhythm of the heart would be fairly regular, but invariably after a few beats the diastolic period would show distinct variations in length; on examination among a large number of tracings which have been taken from this patient since 1900, I have never found one that was regular.

The murmurs due to mitral stenosis.—Concerning the disappearance of the crescendo presystolic murmur, I have to insist upon a fact that has hitherto been overlooked by clinicians, namely, that this murmur is never heard in mitral stenosis after the heart has taken on this disorderly rhythm. Many observers have expressed surprise that the presystolic murmur was absent in cases which showed at the post-mortem examination marked stenosis of the mitral orifice. I must call attention to this possible source of error: that when a diastolic period is short the whole may be filled by the diastolic murmur, and it may be hastily assumed that the murmur is in reality presystolic. This is in a sense true, but there are two points to note in regard to this matter. First, the murmur is invariably diminuendo,

never crescendo; second, if the heart be carefully listened to for a short time a long diastolic period will occur, and if the duration of the murmur be noted it will be found to stop short before the first sound, so that there is a distinct pause between the end of the murmur and the first sound. This peculiarity is indicated in the shading in Figs. 4 and 8. The cause of the diastolic murmur in these cases is, I presume, universally recognized as due to the blood that has been stored up in the auricle during ventricular systole flowing through a constricted orifice as soon as the ventricle passes into diastole. It is therefore a murmur whose intensity gradually diminishes, in marked contrast to the murmur due to the auricular systole whose intensity rapidly increases. In the foregoing case it will be seen that the sudden change in the heart's action presented a disappearance of all clinical evidence of auricular contraction.

Case II. In the following instance a similar series of events took place, but for a time the normal rhythm of the heart was restored. I attended this patient in 1883 for an attack of rheumatic endocarditis. He made a good recovery, and remained in fair health till 1897, when he had serious heart failure. From this also he made a good recovery, and his heart remained perfectly regular till 1904. I have taken tracings of his apex, radial pulse, and jugular pulse at frequent intervals since 1892. His heart was invariably regular except for a short period in 1897, and his jugular pulse was always of the auricular form, a peculiarity in this case being a slight increase in the *a–c* interval, which, however, does not concern the question I am discussing.

Fig. 6 is a tracing of the jugular and radial pulses, and Fig. 7 of the jugular and apex. The rhythm is regular, and the auricular wave, *a*, is well marked. As in the last case, there was here a long diminuendo murmur after the second sound, and a well-marked presystolic murmur (shading in Fig. 8). In the numerous tracings of the apex beat I have taken up to April 19, 1904, there was always a well-marked auricular wave, *a*, preceding the large wave, *v*. When he visited me on the last-named date I found his heart continuously irregular, and on taking tracings of the jugular pulse I found it of the ventricular type, the presystolic murmur had gone, and there was at the time only a diastolic murmur as shaded in Fig. 8. The wave due to the auricular systole had disappeared from the apex tracing. Here, again, with the appearance of the ventricular venous pulse and continuous irregularity all evidences of the contraction of the right and left auricles had disappeared. When this patient called to see me in the following week I found his heart perfectly regular, the auricular wave present in the venous pulse, the presystolic murmur, and the auricular wave in the apex tracing also present (Fig. 9). These conditions continued until November, 1904, when his heart again became irregular and all evidence of auricular systole again disappeared. From that date up to the present the heart has remained in that state, and on the numerous occasions when I have taken long tracings I have never yet found the heart regular for one moment (Fig. 10).

Case III. The patient on whom the following observations were made was under my care in 1880, she then being twenty-nine years of age. She had had rheumatic fever in childhood, and had suffered from mitral stenosis, there being a well-marked presystolic murmur. In 1880 and 1882 I attended her for attacks of rheumatic fever. In 1892 there was considerable enlargement of the liver, which pulsated (Fig. 11).

The character of the pulsation being of the auricular type I concluded that there was also tricuspid stenosis, a diagnosis which was afterwards verified at the post-mortem. This characteristic pulsation of the liver continued until 1898 (Fig. 12, for instance, being taken in 1897), when she had an attack of heart failure, during which time her pulse was rapid and irregular.

When the heart had quieted down the tracing showed a complete absence of the wave due to the auricular systole (Fig. 13).

This patient lived until 1899, and in the numerous tracings taken up to her death the rhythm was never again found regular, nor was there present either the presystolic murmur or the wave in the liver pulse due to the auricle. At the post-mortem examination the auricles were enormously distended, being thin-walled sacs with a few strands of muscular fibre scattered over them. Here, again, the irregularity in the action of the heart was coincident with the disappearance of all signs of auricular systole, namely, the disappearance of the auricular wave from the liver pulse showing the cessation of the action of the right auricle, and the disappearance of the presystolic mitral murmur showing the cessation of the action of the left auricle.

I could demonstrate identical results from the study of many other cases, but I will merely mention one other case of tricuspid stenosis in whom there was a distinct presystolic tricuspid murmur and a presystolic mitral murmur with the auricular forms of pulsation in the jugular vein and liver. The jugular pulse was of great size and force, and the patient was conscious of the movement. One day the patient said to me, 'The beating went from my neck during the night.' When I examined her I found the tricuspid and mitral presystolic murmurs gone as well as the jugular and liver pulsation. All evidences of the systole of the auricle had thus disappeared, and there was for the first time continuous irregularity of the heart's action. A few days later she died suddenly.

Illustrative case with arterio-sclerosis.—So far I have described the inception of this abnormal rhythm in mitral stenosis. Equally instructive and striking is its appearance in certain cases of arterio-sclerosis associated with extra systoles. The form of irregularity produced by extra systoles is extremely common in advanced life, of which Fig. 14 is a good illustration.

Sometimes the small beats due to the extra systoles are missed out. Fig. 14 was taken from a woman aged fifty in 1892. At the same time I took a tracing of the apex beat and of the jugular pulse (Fig. 15).

In the apex tracing there is seen a wave preceding the large ventricular

waves due to the contraction of the left auricle, and in the jugular pulse there is a wave, *a*, due to the contraction of the right auricle. In Fig. 16 the small beats, *o*, in the apex tracing are due to extra systoles, and it will be seen that the premature systole in the apex tracing occurs at the same time as the large auricular wave, *a'*, in the jugular tracing. Here we have an instance of ventricle and auricle contracting simultaneously. I attended this patient at frequent intervals until her death in February of this year. She would be free from extra systoles for a long period, the heart being regular and the jugular pulse of the auricular form (Fig. 17), then there would be periods when she would have them very frequently. In July of 1906 she was suddenly seized with breathlessness and great prostration; I found the heart rapid and irregular in its action (Figs. 1, 18 and 19), and all evidence of the auricular wave gone from the jugular pulse and the apex beat. I have taken a large number of tracings of the jugular pulse with the radial and apex beat, and the jugular pulse was invariably of the ventricular type and the heart continuously irregular (Figs. 18, 19 and 20).

Fig. 20 is a tracing of the jugular pulse and the apex beat, and it is in striking and instructive contrast to Fig. 15. Here again, coincident with the appearance of the irregular action of the heart, all evidence of auricular systole disappeared. (I quote this case specially, as it was the first in which I was able to demonstrate that the extra-systole was due to a premature contraction of the ventricle while the auricle continued at its normal rate.) I could quote a large number of similar instances where this sudden change of the heart's action produced a like result, but they merely illustrate the same features. In several instances while taking tracings these changes have suddenly occurred, and in one or two instances, while a tracing of the jugular pulse was being taken, the heart suddenly reverted to its normal rhythm.

Whereas the main object of this paper is to demonstrate the evidence of a profound change in the manner of the heart's action, there are a few points to which I shall briefly allude, to indicate how this conception of the heart's action leads to certain important and far-reaching conclusions.

What is the auricle doing?—One question that I have been asking for years is, What has the auricle been doing in these cases? Among the first series of post-mortem examinations that I obtained I found such an enormous stretching of the right auricle, with atrophy of the muscular wall, that I concluded that the auricle was paralysed, and I speak in my book on the pulse of 'auricular paralysis'. A long series of post-mortem examinations have shown that in some there is not this great atrophy, certain of the muscular fibres, such as the taenia terminalis, being hypertrophied. From this we can infer that the auricular muscle must have contracted. As from my tracings it was evident that the auricle did not contract at its normal period in the cardiac cycle, I raised the question: Did it contract at the same time as the ventricular systole? When I carefully watched the movements in the

jugular vein of the patient when Fig. 5 was taken, the neck being thin and the internal jugular large, I could see two distinct movements during the period of ventricular systole, one a very rapid and brief movement corresponding with the wave, *a'*, in the jugular tracing, followed by a large movement corresponding to the wave, *v*. The same thing was visible in the patient when Fig. 20 was taken. It was manifest, therefore, that some other factor than the ventricular systole was producing this double wave, and in consideration of all the possible factors one is forced to conclude that the auricle must have contracted at the same time as the ventricle, and that as the contraction of the auricle is much shorter than that of the ventricle, its contraction produced the sharp rise *a'*, and the auricular diastole produced the depression following *a'*. I have carefully considered the question whether *a'* may have been the carotid pulse, but for a variety of reasons, which I will not mention here, I am now convinced that this movement is independent of the carotid. (I have observed in several cases of this class rapid vibratory movements in the veins as at + +, Fig. 10, and I am disposed to think that these movements are due to fibrillation of the auricle.)

Interpretation of the foregoing facts.—In order to account satisfactorily for the manner in which this form of the heart's action arises, I suggest the following line of reasoning. The primitive heart is a tube, the whole length of which possesses identical functions, the most striking being the power of originating a stimulus for contraction, of conveying the stimulus along the tube, and the power of contraction. The contraction starts from the most excitable part, which is normally the venous end. If another part be made more excitable, the contraction starts from that part. In the course of development certain structures are added to the tube. Thus in the frog two parts of the tube are highly differentiated to form the two chambers, the auricle and ventricle. As these differentiated structures mainly serve the function of contraction, the primitive tube gradually loses this power but retains its special functions of stimulus production and conductivity. If a cut be made or a ligature applied (Stannius's first ligature) between sinus and auricle, the sinus will continue to beat and the auricle and ventricle will also beat at a slower rate, but at a rate independent of the sinus. If a cut be made or ligature applied (Stannius's second ligature) between auricle and ventricle, the ventricle will beat at a rate slower than and independent of the auricle. In the human heart the remains of this primitive tube still persist, but greatly modified, though it still retains its functions of originating the stimulus for contraction and of conducting the stimulus. The part which is represented in the sinus venosus of the frog is incorporated in the great veins and in the coronary sinus near their entrance into the auricles. Keith and Flack have lately described near the mouth of the superior vena cava the remains of the sinus portion of the primitive cardiac tube. This is a node of tissue composed of fine delicate fibres into which branches of the vagus and sympathetic nerves pass. Normally it is suggested that the contraction

proceeds from this point, but in dying hearts independent pulsation may be seen starting in the pulmonary veins and coronary sinus, hence it is assumed that part of the primitive tube still persists in these structures. The further remains of this primitive tube are found lower down lying near the *a–v* junction as a node of tissue similar in structure to the sinus node of Keith and Flack. This *a–v* node (Knoten) has recently been very carefully described by Aschoff and Tawara. The node itself is in intimate connexion with the ordinary auricular fibres at one end, and at the other end it passes as a narrow band across the *a–v* junction where it divides into two branches, these pass on to be distributed, the one to the left ventricle, the other to the right. After leaving the node of finely reticulated tissue the histological character of the bundle alters, the cells becoming larger and partially striated. The retention in the mammalian heart of the functions peculiar to the primitive tube is inferred from experiments where this bundle has been divided after it leaves the auricle. In such instances, while the auricle continues beating at its normal rate, the ventricle has a slower and independent rhythm, just as happens in the frog's heart after the second Stannius's ligature. In man the condition known as Stokes-Adams Disease is due to a blocking of these fibres between the auricle and ventricle. The suggestion that I make is that in advanced cases of mitral stenosis the distension of the auricles interferes with the conduction of the stimulus, so that a break is made between the sinus node and the *a–v* node, a condition resulting similar to that which happens in the first Stannius's ligature. This view finds support in the post-mortem examination of these cases, the auricle being often enormously distended. In Figs. 22 and 23 Dr. Keith has drawn two hearts to compare with the heart of Case I.

It is also well known that when a stimulus is applied so as to make one portion of the heart more excitable than the rest the contraction will proceed from that point. As in all the cases where this abnormal rhythm has occurred apart from rheumatic endocarditis, there has been found marked degeneration of the coronary artery, particularly of that branch of the coronary that supplies the *a–v* node and bundle. The nodal tissue in such cases has been found with an increased number of nuclei and an increase in the fibrous tissue. I suggest therefore that this evidence of degeneration implies greater irritability, and in consequence the tissue of the *a–v* node becomes more excitable than that of the sinus node, and in accordance with the law of increased excitability the contraction of the heart proceeds from this point. The extension of the sclerosis in old rheumatic cases may lead to a similar result. The direct experimental stimulation of these fibres has not yet been satisfactorily demonstrated. Keith states that the auriculo-ventricular ring in the heart of the lower animals is identical with the *a–v* node in the human heart. Gaskell[3] has stimulated the *a–v* ring in the tortoise and found

[3] Gaskell, W. H., Article: 'The Contraction of Cardiac Muscle', in *Schäfer's Physiology*, vol. ii, p. 179.

that whereas any other portion of the ventricular muscle responded to a single stimulation by one beat, when this ring was touched a rapid series of contractions followed. McWilliam[4] and H. E. Hering[5] have also demonstrated that the contraction of the mammalian heart can arise elsewhere than at the mouths of the great veins, and that the ventricles contract before auricles, or auricles and ventricles contract simultaneously.

Results of this abnormal inception of the cardiac rhythm.—When this abnormal rhythm is set up there is at once a limitation of the field of response to effort, the heart being placed at a disadvantage in carrying on its work. If the heart muscle itself be in good condition little effect may be shown beyond a slight limitation of the field of cardiac response. If pre-existing conditions have weakened or injured the muscle then heart failure more or less severe may at once result. In severe cases where the heart muscle is much degenerated severe symptoms of cardiac failure may appear in a few hours, and if no relief is obtained death may follow in the course of a few days or a few weeks. If the condition yields to treatment the patient may live a life with limited power for years. Should the heart revert to its normal rhythm, the rapid disappearance of all signs of heart failure is remarkable. The response of these hearts to digitalis is most interesting and important. If, for instance, the condition is secondary to a rheumatic endocarditis, as a rule the heart responds to digitalis very readily. Some of these hearts one can play upon with digitalis, making them slower or quicker at will. On the other hand, when the abnormal rhythm is secondary to arterial degeneration, then digitalis has very little effect, and in some cases none at all.

Since I made the foregoing communication to the Association of Physicians my attention has been called to some other evidence, confirmatory to a certain extent of both the views I have suggested. Dr. John Hay pointed out to me an article in which Lohmann[6] claims to have stimulated the *a–v* bundle at or near the *a–v* node. As the result of such stimulation the auricles and ventricles contracted simultaneously.

Professor Erlanger[7] has sent me a paper in which he cites the results of a series of experiments on the different places in the heart where the stimulus for contraction arises. In one series of experiments severe injury to the region of the great veins caused the rhythm of the heart to

[4] McWilliam, John A., 'On the Rhythm of the Mammalian Heart.' *Journal of Physiology*, vol. ix, p. 185.

[5] Hering, H. E., 'Zur experimentellen Analyse der Unregelmässigkeiten des Herzschlages.' *Archiv für die ges. Physiologie.* Bd. 82. Bonn, 1900. Fig. VIII, Tafel III.

[6] Lohmann, A., 'Zur Automatie der Brückenfasern und der Ventrikel des Herzens.' *Physiolog. Abtheilung des Archives für Anatomie und Physiologie.* Leipzig, 1904. S. 431.

[7] Erlanger, J. and Blackman, J. R., 'A Study of Relative Rhythmicity and Conductivity in various regions of the auricles of the Mammalian Heart.' *American Journal of Physiology*, vol. xix. June 1, 1907. No. 1, p. 167.

change, the ventricle no longer following the auricle, but auricle and ventricle contracting simultaneously. This corresponds to what I have suggested when there is great auricular distension in advanced mitral stenosis. Erlanger, however, gives a different explanation, suggesting that the stimulus from some abnormal source is blocked, so that its conduction to the auricle is slower than its conduction to the ventricle, with the result that the ventricle contracts at the same time as the auricle. It is difficult for me to appreciate the grounds on which he makes this suggestion; he seems to have overlooked the peculiar nature of the *a–v* node, and I do not think his explanation can be accepted until he has considered the other possibilities. His view that the *a–v* bundle is merely a conducting system is demonstrably wrong. It must be remembered that the sections of the bundle in the living heart that he and Hering have made were below the *a–v* node, so that the experimental investigation of this node has yet to be undertaken. In cases of heart block the lesion generally destroys this node and the adjacent portion of the bundle. The remaining portion of the bundle continues active, creating the stimulus and sending it on into the ventricles. Thus Dr. Keith tells me that in a case of heart block where the block had existed for eighteen years the bundle below the seat of destruction was in every particular perfectly healthy. Had this bundle merely the function that Erlanger attributes to it, it must have atrophied, but seeing it was healthy eighteen years after it had ceased to convey the stimulus from auricle to ventricle, it must have had some other function, and, reasoning by a process of exclusion, one is forced to recognize that this bundle can create as well as conduct a stimulus.

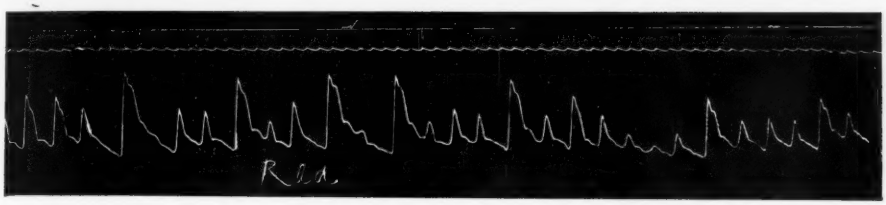


FIG. 1. Tracing of the radial pulse showing the irregularity characteristic of the sudden inception of the rhythm of the heart by the irritated *a-v* node (from Case IV, July 7, 1906).

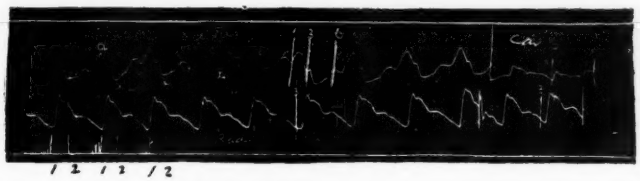


FIG. 2. Simultaneous tracings of the jugular and radial pulses in the first part, of the carotid and radial in the latter part. The jugular tracing shows the form characteristic of the auricular venous pulse where the wave, *a*, due to the auricle precedes the carotid wave, *c* (downstroke 3). The shading underneath represents the time of the presystolic murmur (Case I, Nov. 5, 1895) [1].

[1] The letters and figures in all the tracings have the same significance.

a = wave due to auricular systole.
c = „ „ carotid pulse.
v = „ „ stagnation of blood in auricle and veins during ventricular systole. The fall of *v* corresponds to the opening of the tricuspid valves (downstroke 6).
x = fall due to auricular diastole, &c.
y = „ „ ventricular diastole.

The downstrokes represent—1, the beginning ot auricular systole; 2, the beginning of ventricular systole; 3, the beginning of the carotid pulse; 4, the beginning of the radial pulse; 5, the closure of the semilunar valves; 6, the opening of the tricuspid valves.

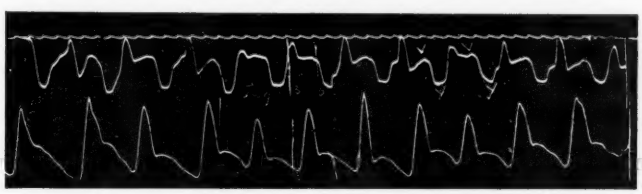


FIG. 3. The jugular pulse is now of the ventricular form—no auricular wave precedes the downstroke 3, and the rhythm is irregular (Case I, March 19, 1904).

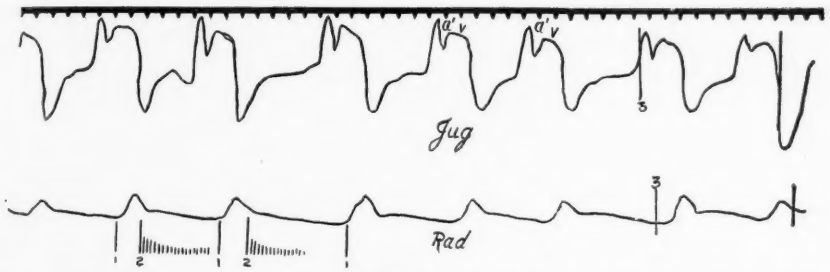


FIG. 4. The jugular pulse is of the ventricular form, and *a'* is probably due to the auricular systole occurring at the same time as the ventricular systole (Case I, Dec., 1906).

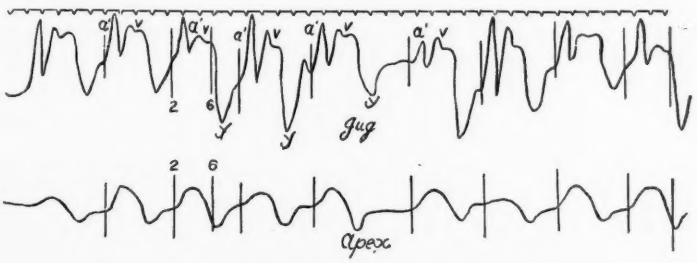


FIG. 5. The jugular pulse and apex beat (Case I, Feb., 1907).

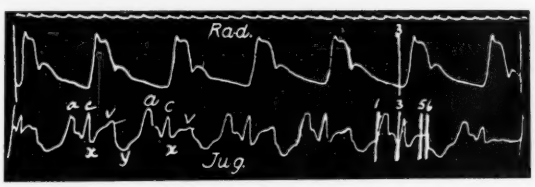


FIG. 6. The jugular pulse is of the auricular type, and the rhythm is regular (Case II, Nov. 29, 1903).

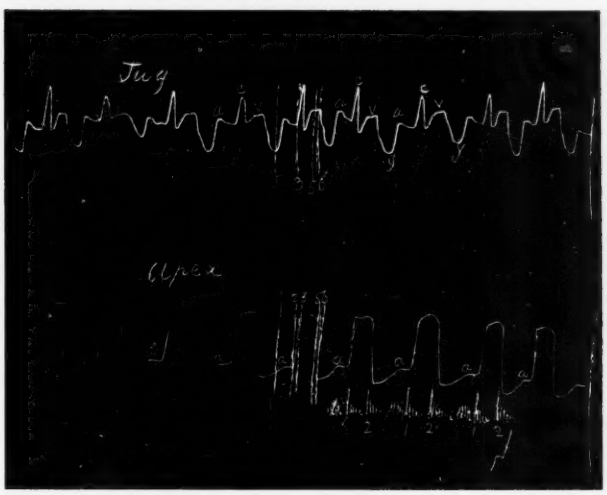


FIG. 7 shows a well-marked wave in both jugular and apex tracings due to the auricle (*a*) (Case II, March 20, 1904).

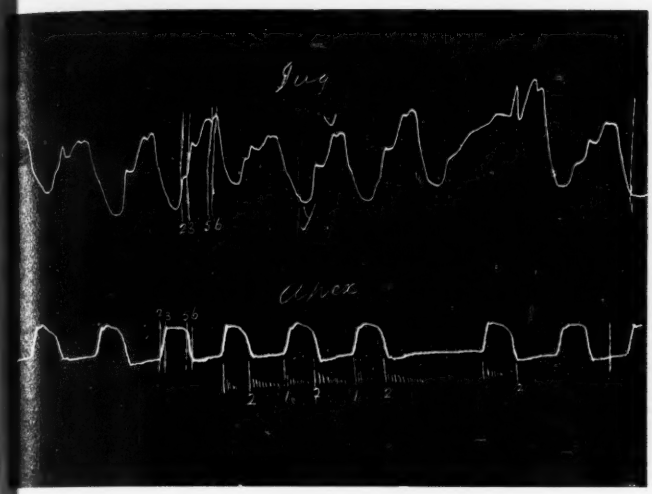


FIG. 8. The rhythm is now irregular, and there is no wave in either jugular or apex tracing due to the auricle. The shading under the apex tracing shows a diastolic murmur, and no murmur due to the auricular systole as in Fig. 6 (Case II, April 19, 1904).

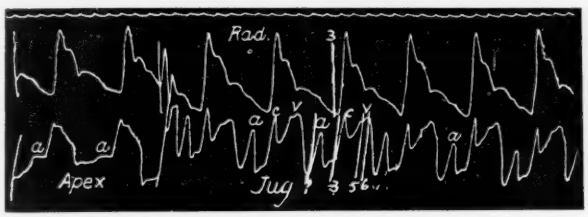


FIG. 9. Taken a week after Fig. 8, and shows a regular rhythm and a wave both in apex and jugular tracings due to the auricular systole (Case II, April 26, 1904).

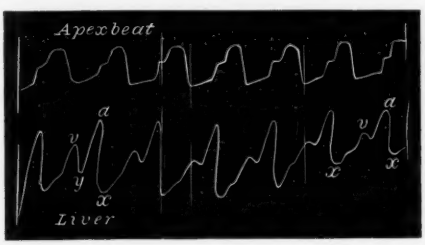


FIG. 11. The principal feature in the liver pulse is the large wave, *a*, due to the auricular systole (Case III, 1892).

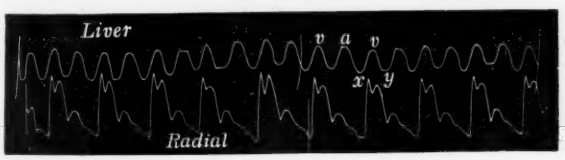


FIG. 12. The wave, *a*, due to the auricular systole, is still a marked feature in the liver pulse (Case III, 1897).

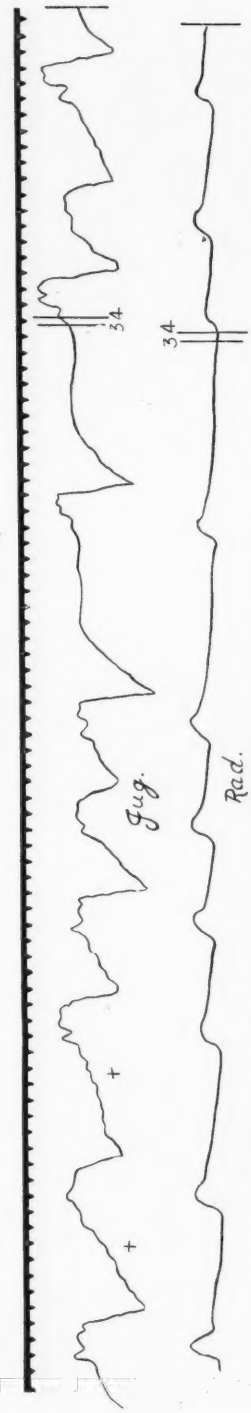


FIG. 10 shows an irregularity which has been continuous since November, 1904. The jugular pulse is of the ventricular type, and at + and + are a series of small waves that I suggest are due to fibrillation of the auricle (Case II, March, 1907).

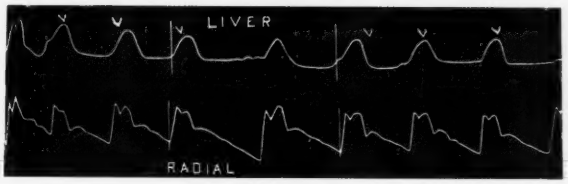


FIG. 13. The rhythm is irregular, and the waves due to the auricular systole, which are such prominent features in Figs. 11 and 12, have now disappeared (Case III, 1898).

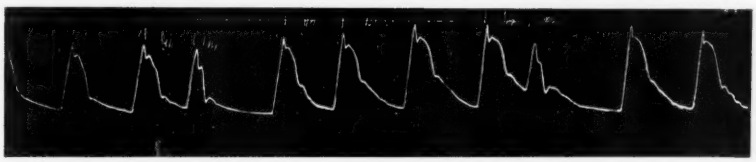


FIG. 14. Radial tracing showing small beats due to the premature contraction of the ventricle (extra systoles) (Case IV, 1892).

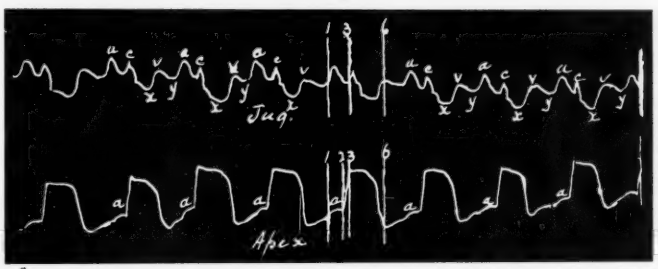


FIG. 15. In both jugular and apex tracings are well-marked waves, *a*, due to the auricular systole (compare with Fig. 20) (Case IV, 1892).

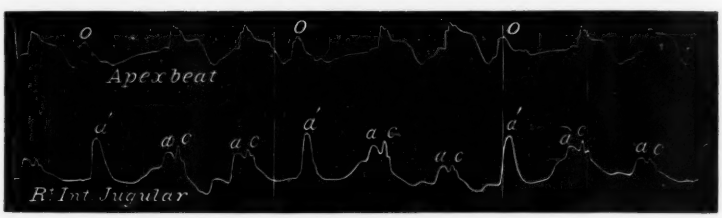


FIG. 16 shows premature contractions of the ventricle, *o* (extra systoles), in the apex tracing, while in the jugular tracing are shown waves, *a'*, due to the auricular systole occurring at the same time as the premature ventricular contractions (Case IV, 1892).

FIG. 17. The rhythm is regular and the jugular pulse of the auricular form (Case IV, 1903).

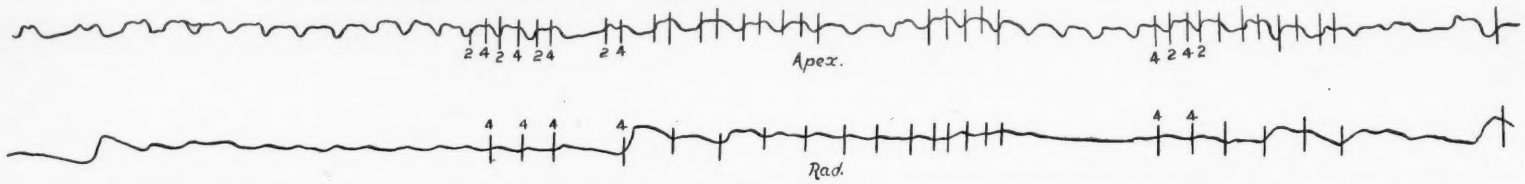


FIG. 18. Apex and radial tracings showing the characteristic increased rapidity and irregularity which appears on the starting of the heart's contraction at the irritated *a-v* node (Case IV, July 7, 1906).

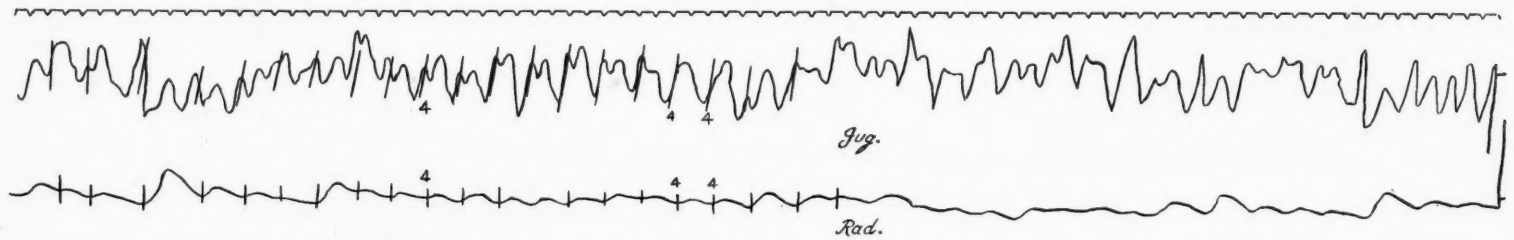


FIG. 19. The jugular tracing suddenly becomes of the ventricular type, as shown here (Case IV, July 7, 1906).

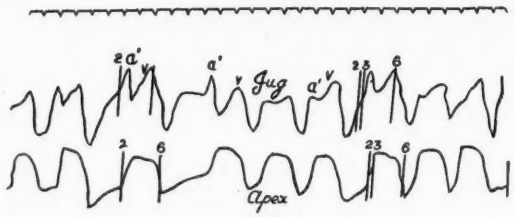


FIG. 20. Jugular and apex tracing when the heart has slowed down. Note the disorderly rhythm and the entire absence of the auricular wave at the normal period of the cardiac cycle. I suggest that *a'* is due to auricular systole occurring at the same time as the ventricular systole. Compare with Fig. 15 (Case IV, Dec., 1906).

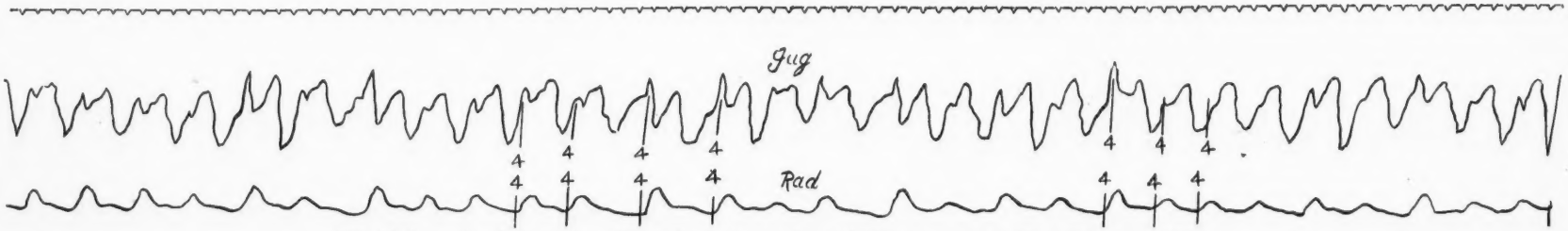
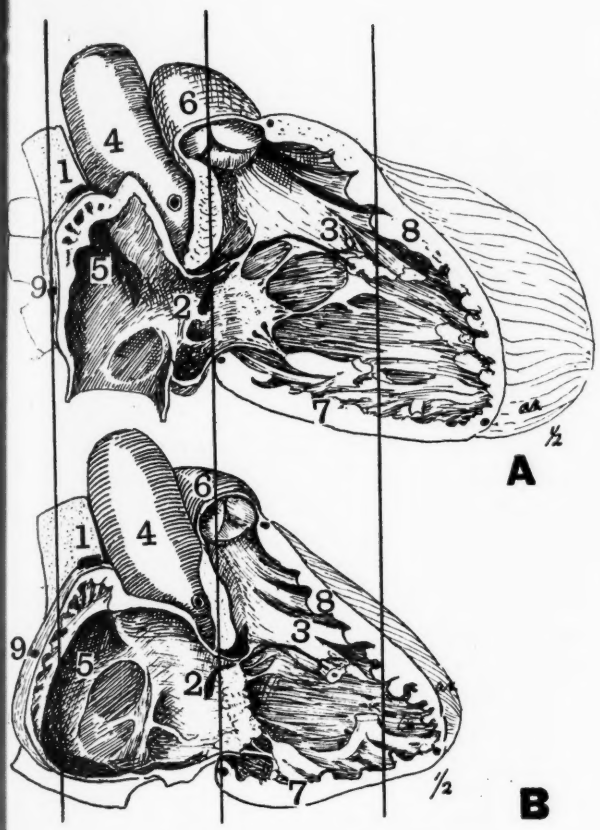


FIG. 21 shows the characteristic disorderly rhythm and ventricular venous pulse (Case IV, Dec., 1906).

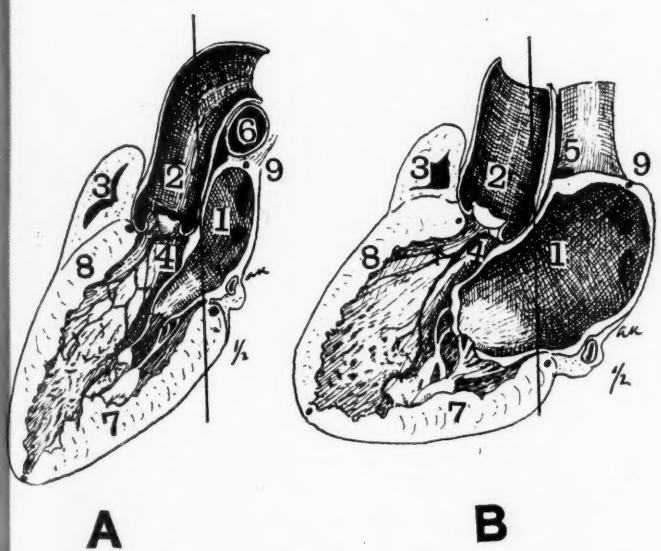


A. Heart of a man in whom the rhythm was normal, the septal wall of the right auricle and ventricle being exposed (half natural size). It shows ventricular hypertrophy with auricles nearly normal in size.

B. Heart of Mrs. P. (Case I) exposed in a similar manner. It shows auricular distension—dilatation with compression of the ventricles.

1. Superior vena cava above the sino-auricular node.
2. Auricular canal above the base of the septal cusp, where the *a–v* node is indicated with the *a–v* bundle running from it.
3. Moderator band, at the junction of the infundibulum and the sinus of the right ventricle, indicating the position of the right septal division of the *a–v* bundle.
4. Aorta.
5. Right auricle below the superior caval orifice and the taenia terminalis.
6. Pulmonary artery.
7. Diaphragmatic wall of the right ventricle; its length is measured between the points indicated in the diagram.
8. The sternal wall of the right ventricle: its length is measured between points indicated; in compression of the ventricle it is the diaphragmatic wall which is shortened (compare A and B).
9. Point from which the length of the right auricle is measured—to the point at base of diaphragmatic wall of right ventricle. Compare these measurements—A and B.

FIG. 22. CONTRASTED TYPES OF HEART. (KEITH.)



A. Normal heart with the left auricle and ventricle exposed.

B. Dilated left auricle and compressed left ventricle (Mrs. P., Case I).

1. Left auricle.
2. Aorta—laid open.
3. Infundibulum of the right ventricle.
4. On septal wall of the left ventricle, in front of the mitral and behind the left septal division of *a–v* bundle.
5. Superior vena cava (B) with the position of the sino-auricular node indicated from the left side.
6. Right pulmonary artery.
7. Diaphragmatic wall of left ventricle, the points of measurement are indicated.
8. Sternal wall with points of measurement.
9. Upper attachment of the left auricle; its height is measured from the point indicated to that on the base of the diaphragmatic wall.

FIG. 23. CONTRASTED TYPES OF HEART. (KEITH.)

ON HAEMATOPORPHYRINURIA NOT DUE TO SULPHONAL

By T. K. MONRO

The subject of haematoporphyrinuria presents itself for consideration under three aspects:—

(1) In the first place, as Garrod[1] has shown, haematoporphyrin may be regarded as being, in minute traces, a constant constituent of normal urine.

(2) In the second place, haematoporphyrin is frequently present in the urine in increased quantity in disease, but without being associated with any obvious change in the colour of the urine. This form of haematoporphyrinuria is met with in many ailments, and was first described by MacMunn[2] in connexion with a case of rheumatic fever.

(3) In the third place, a great excess in the amount of haematoporphyrin may be associated with a distinctly abnormal colour of the urine, which may be pink, red, magenta, brownish red, dark brown, or almost black.

The third class of cases just described may be divided into two sub-classes. (i) The first and larger sub-class consists of cases where the haematoporphyrinuria is a symptom of intoxication by a drug, usually sulphonal, but in some instances trional or tetronal. This symptom is an evil omen, and should be regarded by the physician as a danger-signal. (ii) The second sub-class is much smaller, and consists of rare cases which occur apart from the use of drugs. In this group the abnormal condition of the urine seems not to be in itself of any very grave significance. It has come under observation in connexion with a variety of diseases, and has occasionally been met with under circumstances which show that haematoporphyrinuria may occur in an intermittent or paroxysmal form, analogous to paroxysmal haemoglobinuria. Or again, the condition may persist for many years.

The three cases now to be mentioned belong to this second sub-class. The examinations of the urine were made by Dr. D. F. Riddell.

Case I.—*Periodic Vomiting of Childhood, Acetonuria, Haematoporphyrinuria.*

W. S., a schoolboy, aged 7, was seen in consultation with Dr. McLelland of Alexandria, on December 20, 1906, on account of obstinate vomiting. During the preceding two years he had been subject to cycles of vomiting which occurred at least once every two months. Each cycle lasted for about two weeks, as a rule; but the one in which I saw him was exceptional, since it had already lasted for three weeks, with two breaks of about five days each. The approach of a cycle was sometimes heralded for a day or two by anorexia and malaise, and in one attack there was jaundice. In the earlier attacks

he got soda-water and white of egg by the mouth, and he seemed to benefit from the administration of calomel in half-grain doses till free action of the bowels took place. But in the later periods of vomiting the stomach would retain nothing, and any food that he got had to be administered by the rectum. Under these circumstances he lost weight considerably, but after the paroxysm passed off, he would rapidly regain his former condition. He had a very severe attack of diphtheria between two vomiting cycles, a year before I saw him, and at the best he was a delicate child.

A detailed examination, in the present or latest cycle, revealed no definite evidence of organic disease. The heart, lungs, liver, spleen, and superficial lymph-glands all seemed to be healthy. The urine was normal, and the fundi, so far as could be seen, were also healthy. There was a slight hint of Kernig's sign on each side. The boy slept well; had no discharge from the ear; and, so far as was known, had received no injury to his head before the tendency to vomit showed itself. About a week before these observations were made he had pain in the left ear followed by transient parotitis.

On the day after the consultation the boy was very ill, and was passing blood by the bowel. The vomitus was coloured like coffee, and had a total acidity of 56, but gave no reaction for free acid. On the following day, and indeed for several days about this time, the urine contained a trace of albumin. About the beginning of this year the cycle was interrupted by a third break of five days with freedom from vomiting. The pulse and temperature were normal, and the urine was again free from albumin.

A specimen of urine received on January 8 was noted as free from albumin and blood, but it gave distinct reactions for acetone and diacetic acid.

On January 15 the urine, for the first time, looked like blood, but it yielded practically no sediment, it gave no reaction with guaiac, and it gave no definite reaction for albumin. Examination by Dr. D. F. Riddell showed the presence of haematoporphyrin. Meanwhile the temperature continued normal; the pulse ran about 80 or 84; there had been no vomiting for three days; the bowel retained peptonized enemata quite well; and two or three attacks of flatulent colic, which had occasioned distress, were relieved by rectal injections containing turpentine.

This abnormal pigmentation of the urine continued until the boy died on January 22, 1907. By this time he was greatly emaciated. He had been free from vomiting for about six days before the end, but towards the close he threw up some blood on one or two occasions. At no time were drugs of the nature of sulphonal or trional administered.

CASE II.—*Pelvic Exudate, Multiple Neuritis, Haematoporphyrinuria.*

Mrs. McL., aged 36, was seen on April 15, 1907, in consultation with Dr. Stewart Campbell. She had been seized about five weeks previously with pain in the abdomen, especially over the liver and kidneys, together

with vomiting. It is believed that the abnormal colour of the urine appeared at this time. Two days afterwards a pelvic exudate became recognizable. It could be felt about the brim of the pelvis in front, chiefly, though not solely, on the right side. The temperature was noted as high as 102°. The pulse rate was over 120, and the tachycardia continued for some time after the pyrexia subsided. Even in sleep the pulse rate might be over 110.

By the time I saw the patient the exudate had disappeared, but the urine continued to show its abnormal colour. It had been repeatedly tested for albumin, but always with a negative result. A specimen which Dr. D. F. Riddell was kind enough to examine gave the tests for haematoporphyrin with a suspicion of urobilin.

This patient had been troubled with constipation, but scybala were got rid of under appropriate treatment. In the latter part of this illness she had suffered from pains in the legs, and it was now observable that between the knees and ankles the muscles were flaccid, wasted, and tender. It was natural to attribute these phenomena to pressure on nerves by the pelvic exudate, particularly as the right leg was worse than the left. But some doubt was thrown upon this explanation, not only by the fact that she had slight crampy pains in the arms, but still more by the fact that when she had so far recovered as to move about at her household duties, she found that the extensors of the right upper limb were involved in a similar manner.

It should be added that a detailed examination of the blood showed a slight deficiency of the haemoglobin, and a slight increase in the leucocytes, but otherwise no noteworthy change. The knee-jerks were retained.

Two days after the facts already mentioned were noted, it was found that Kernig's sign was well marked.

On May 1 Dr. Campbell informed me that the urine had of late been clearing up, and that Kernig's sign was passing away. After a few days more the patient was able to leave town for a change.

In this case there was no reason to suspect alcoholism, while drugs of the sulphonal type could be excluded.

CASE III.—*Paroxysmal Haematoporphyrinuria in a Patient whose Urine contained free Haemoglobin and reduced Fehling's Solution.*

J. McN., aged 26, became chilled while bathing in the sea in July, 1906, and vomited shortly afterwards. She paid no attention to the urine till a week afterwards, when she observed that it had a red colour.

I shall not describe this case in detail in the meantime, because I hope that this will be done by Dr. H. H. Borland, under whose care the patient is, and who is still carrying out the investigation of the urine. But I may add that the urine in recent times has not only presented a remarkable variety of colour on different days, but has on one or more occasions given a reaction for sugar or for haemoglobin.

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Why haematoporphyrin or iron-free haematin should be present in excess in some urines is still a mystery. One was naturally tempted by the co-existence of a pelvic exudate in Case II to think of extravasated blood as the source of the pigment. But in this case the abnormal condition of the urine was supposed to have been present from the beginning, and not simply while the exudate was being absorbed. Moreover, the results of the blood examination gave no support to the theory of excessive blood destruction. The same question arose in connexion with a case recorded by Sobernheim[3] in 1892. The patient was a boy who was suffering from enteric fever, and who was also the subject of haematoporphyrinuria. He developed a haematoma of the rectus abdominis muscle, which in its evolution and decline corresponded in a rough way with the abnormal colour of the urine. But further investigation showed that the urine contained an abnormal amount of haematoporphyrin for weeks after its colour had become clear. And it was also ascertained that for years past the urine had at times been characterized by a peculiar colour. These facts are quite in accordance with Garrod's conclusion[4] that excessive haematoporphyrinuria is due to a perversion, rather than an increase, of haemoglobin catabolism.

When certain facts are borne in mind, it is evident that the term haematoporphyrinuria as applied to these abnormally-coloured urines is but a provisional designation. Hammarsten[5] showed that other abnormal pigments are present in these urines; Sobernheim[6] showed that the haematoporphyrinuria may persist after the abnormal colour has almost disappeared; and Garrod[7] showed, on the one hand, that the haematoporphyrin may be removed from a urine of this kind without materially altering its colour, and, on the other hand, that a corresponding amount of haematoporphyrin may be added to a normal urine without producing more than a trifling change in its colour. The inference is that the pink, red, purple, or brown colour of the urine in cases of haematoporphyrinuria is due mainly, if not solely, to other pigments than haematoporphyrin; and what is now much to be desired is the discovery of some means whereby we can identify those other pigments, which appear to possess no characteristic spectrum.

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Further references will be found in von Jaksch's *Clinical Diagnosis*, 1905, fifth English edition, edited by A. E. Garrod.

ON MULTIPLE HEREDITARY TELANGIECTASES WITH RECURRING HAEMORRHAGES

By WILLIAM OSLER, M.D., F.R.S.
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With Plates 10, 11

Strictly speaking, telangiectasis is a dilatation of the terminal vessels, i. e. of the capillaries, but we use the term also to describe dilated venules. While applied most correctly to the congenital condition, the term naevus is sometimes used for the acquired form. Telangiectases occur on all parts of the skin. We see them under the following conditions: (1) On the cheeks, the nose, and the ears in persons who are exposed to the weather, and in heavy drinkers; but this Rosacea, as it is called, may be present also in young persons and be a source of much distress. A very interesting form is that so often seen as aborescent, distended venules on the skin of the thorax along the line of the attachment of the diaphragm.

2. Small pinkish spots from two to five millimetres in diameter, perfectly smooth and uniform, without visible venules, which disappear completely on pressure. These may be not more than a pin point in size, and they often have a vivid pink colour. They may appear suddenly and last for several years and then disappear.

3. The small nodular forms, raised and of a bright crimson or purple colour, varying in size from one to five millimetres. They may be congenital, and there are few bodies on which they are not seen, but with the patches of pigmentation and the yellow, plague-like warts they form common senile changes in the skin of every one above sixty years of age. A point of interest is their supposed connexion with cancer of the abdominal organs, particularly of the stomach, but they are so common in old persons and in so many different conditions that the association is probably only accidental.

4. The spider form, made up of a central dot, sometimes raised and nodular, from which radiate five or six venules, or more correctly, towards which these vessels converge. This, the so-called *naevus araneus*, is seen on the skin of the eyelids and on the cheeks of children and young girls, and by its vivid colour may be very disfiguring.

The most interesting association of the spider naevus is with cirrhosis of the liver. In no other condition may we watch the development of such remarkable telangiectases. The typical form in this disease is a plaque, ovoid or circular, two to three centimetres in diameter, of a pink or dark purple colour due

[Q. J. M., Oct. 1907.]

to a diffuse dilatation of the capillaries, and across these plaques spider veins converge to a nodular centre. In some instances there are no visible veins, only a rosy red circular spot with a darker centre. On the forehead and cheeks there may be four or five. I have counted a dozen or more scattered over the arms and trunk. They do not appear to have any relation to jaundice. A remarkable circumstance is their complete disappearance without any change in the condition of the patient. They are met with also in organic disease of the liver, but are not so frequent as in cirrhosis, of which they may indeed be a diagnostic indication. One patient had troublesome bleeding from a spot, the nodule of which he had scratched. An interesting instance occurred in a medical student in connexion with an attack of catarrhal jaundice. A dozen or more of these spider naevi appeared on his face, and after persisting for three or four months gradually went away. Remarkable spider naevi occur on the scars of the X-Ray burns, and they may appear in enormous numbers on the skin in scleroderma.

5. The mat form. Among the most remarkable acquired variety is that which may be well called by this name, as it represents a large area of the skin, $1\frac{1}{2}$ to 4 inches in extent, which becomes involved in a capillary telangiectasis. At a distance the spot looks like an abrasion or an area of intense hyperemia, but on close inspection with a lens the smaller vessels of the skin are seen to be uniformly dilated. The colour is often of a vivid pink, but without the depth or intensity of the common birth-mark. This form, too, I have seen in cirrhosis of the liver and once in leukaemia.

6. The generalized, acquired telangiectases—the *télangectases essentielles en plaques* of the French—a form in which there appear in large numbers over the trunk or extremities numerous stellate venules. This is a rare form, of which only some fifteen or sixteen cases are on record. I have reported a case in the Johns Hopkins Hospital Bulletin for this year.

And lastly, *the multiple hereditary form with recurring haemorrhages*, which is the special subject of this paper.

In the Johns Hopkins Hospital Bulletin, vol. xii, I reported the history of two brothers who had numerous telangiectases of the skin and mucous membrane, and who had had from childhood bleeding from the nose and from some of the spots. Seven members of the family had been subject to it. The bleeding had usually been from the nose, on the mucous membrane of which spider naevi could be seen. One of the brothers died under my care, and telangiectases were found in the mucous membrane of the stomach, as well as in that of the nose. The third case, reported in the same paper, has been under my observation on and off since 1896. He had had attacks of bleeding from the nose from his tenth year, and from the telangiectatic spots on the gums and lips. The bleeding has been profuse, and he has frequently had to have the nostrils plugged. I saw this patient last in January, 1907. He had only recently recovered from a severe attack. The appearance of his face was very much like that given in the coloured illustration of Dr. Kelly's patient (see Plate 11), and the representation of part of his face is given in Plate 10. I had not seen him for

three years, and, though very numerous, the spots were smaller and some of them had disappeared. One special change had occurred in the ten years he has been under observation, in the more nodular character of some of the spots, so that many now form definite naevi raised two or three millimetres above the level of the skin. No members of his family have been subject to the trouble. I have here to report another family, and shall analyse briefly the literature of a subject which has attracted some attention since the appearance of my paper in 1901.

Family X.—In the summer of 1904 I was called to New York to see a patient with Dr. ——, aged 53, who had been in active practice for more than twenty-five years. I was at once attracted by his pallor, and the presence of numerous telangiectases of the skin of the face, ears, and lips, all of which stood out with great clearness on account of the anaemia. He stated that for years he had been a bleeder, chiefly from the nose, but also from the spots. The bleeding had begun at his tenth year, and it had been a source of constant distress from his youth. Though usually from the nose, he had bled from the spots on the skin of the face and of the head, once badly from a spot on the arm, and very frequently from the mucous membrane of the mouth. Within the past year the bleeding has been very profuse, scarcely a day passing without loss of blood. I saw at once the resemblance of the case to those I had already reported. I asked about the family history, and he said that he belonged to a bleeder family, that his grandfather, father, and one sister had had the spots, and had bled in the same way, and that his son, a young man of twenty, had had occasional epistaxis, but no spots. He regarded the condition as one of haemophilia. Fortunately, he fell into the hands of my friend, Dr. Coe, who has reported the case in the Journal of the American Medical Association, October 6, 1906. I saw Dr. —— in January, 1907, and was at once impressed with the remarkable improvement in his appearance. He was no longer anaemic, the spots were much less marked, and he told me that by Dr. Coe's advice he had begun to take calcium lactate, 20 grains three times a day, and he had had some of the more prominent spots on the face touched with the electric needle. For more than a year he had scarcely had any bleeding. The coagulation time, which had been to six or seven minutes, had been lowered to a minute and a half. He had gained in strength and weight, and felt in every way better than he had done for years. The other members of his family, who have been affected, have bled in just the same way from the spots alone or from the nose, never from the cuts, and have never had joint troubles as in ordinary haemophilics.

The telangiectases in this condition are of three sorts—the pin point, which may be readily overlooked and which may be numerous on the skin of the hands or of the face; the spider form, which is most common; and the nodular variety, which may gradually arise in the centre of a spider naevus and form a solid, vascular tumour the size of a split pea. The coloured illustrations here annexed show at a glance the very characteristic condition. I am much indebted to Dr. Kelly for allowing me to reproduce the illustrations of his case.

At least eight families, the subject of this peculiar affection have been recognized: *Family I.*—Wickham Legg [1]—Man aged sixty-five, in whom numerous naevi had appeared over the face and parts of the trunk; first noticed after his fortieth year. He had had epistaxis from boyhood, and had bled from slight traumatism. One sister, a son and a daughter had suffered from epistaxis. Legg reports the case as one of haemophilia. *Family II.*—Chiari [2]—The case of two sisters with multiple telangiectasis of the skin and mucous membrane. They had also relatives who were subject to epistaxis, and the sisters are said never to have bled much from cuts. I have not been able to consult Chiari's paper in the original as it is not in any of the libraries accessible. *Family III.*—Rendu—When I reported my paper the only cases at all similar that I could find are those reported by this author [3]—a man aged fifty-two, whose mother and brother had been subject to epistaxis, was admitted in a condition of profound anaemia, having had for three weeks a daily recurrence. He had bled from the nose at intervals since the age of twelve. On the skin of the face and on the mucous membrane of the lips and mouth were numerous small telangiectases. *Family IV.*—Kelly [4]—Two sisters with the characteristic telangiectases of the face and mucous membrane, recurring bleedings, usually from the nose. One sister bled from the spots on the tongue and lips. The elder sister died of syncope induced by a severe and persistent epistaxis. *Family V.*—Hawthorne [5]—Woman, aged forty-nine, repeated epistaxis from childhood with multiple telangiectases. The father, the sister and the eldest daughter had small spots on the skin, and her nine children had had attacks of epistaxis, but apparently only one had had the spots. *Family VI.*—Parkes Weber [6]—The patient, a woman (shown at the first meeting of the Association of Physicians in May), aged sixty, presented very characteristic condition of the face and mucous membranes. She had had repeated bleedings from the nose, never from any of the other spots. The telangiectasis appeared when she was forty-two, a few years after the onset of the epistaxis. The mother had epistaxis, and spots on her face. Of the patient's nine children three sons and one daughter have epistaxis, and two of the sons have multiple angiomata of the skin and mucous membrane. *Family VII.*—Osler—Two brothers, aged fifty-five and fifty-seven. The father had had bleeding from the nose from boyhood. One sister had bled from the nose and one from both nose and mouth. The niece and the grandniece also had epistaxis. *Family VIII.*—Osler—The family here reported, four members of which have been affected. And lastly, there is the case of the man referred to in this paper, in whose family, so far as we know, there has been no epistaxis and no spots. I have not included the family reported by Babington (*Lancet*,

[1] *Lancet*, 1876, vol. ii, p. 856.

[2] O. Chiari, *Erfahrungen auf dem Gebiete der Hals- und Nasenkrankheiten*, S. 60 et seq., Wien, 1887.

[3] *Gaz. des Hôpitaux*, 1896.

[4] *Glasgow Medical Journal*, June, 1906.

[5] *Lancet*, 1906, vol. i.

[6] *Lancet*, 1907, vol. ii.

1865, ii.) as the patients had only epistaxis, and there was no reference to telangiectasis.

The disease is one of very serious character, as the bleedings are often of great severity, and in some of the cases have recurred with such frequency that a state of chronic anaemia has been produced. My first patient, Mr. C., stated with his quiet humour that 'he had been in the habit of bleeding to death', and on several occasions he returned to the hospital profoundly anaemic with swelling of the face and oedema of the feet. One of Dr. Kelly's patients died in syncope following a haemorrhage. In the great majority of the cases the bleeding is from the nose, and has the usual character of epistaxis. In other instances the blood comes from the spots on the lips, the tongue, gums, and mucous membrane of the palate. Only in a few instances has the bleeding been from the spots on the skin, and once from spots on the scalp. One of the cases bled severely from a spot on the arm.

From the nose the bleeding takes place spontaneously. It is easy to understand how the picking of the nostrils or violent blowing of the nose would cause rupture of the dilated, thin-walled vessels. In one of my cases a section of the mucous membrane of the septum was made, and a large number of dilated veins were found just beneath the epithelial layer. From the lips, tongue and gums a slight traumatism in the act of eating is the usual cause. It is more particularly when a central portion of the spider naevus is raised as a small nodule that the bleeding is likely to occur. In one of the cases there were a dozen round foci, each from three to four millimetres in diameter, in the mucous membrane of the stomach, but though cancer was present, there had been no active haemorrhages. None of the patients appeared to have any tendency to spontaneous haemorrhages, except Wickham Legg's, and in this case there is only a general statement to this effect.

While the telangiectases may occur early in life, as in my third case, as a rule they are not noticed until later, and in other cases apparently they follow the epistaxis. It is quite possible that the condition of anaemia induced thereby may be a factor in the development of the angiomota, which certainly vary a great deal in size and even in number from time to time. In Case III of my series the patient stated that the spots were always less noticeable after he had had a freedom from severe bleeding for some months. When I last saw him in January of this year the spots on his face had diminished greatly in size.

That severe bleeding may occur from a small naevus is well known. I saw an instance in a case of chronic Bright's disease in which the patient bled from a little naevus on the lip. He subsequently had diffuse purpura. Dr. William Bligh [7], of Caterham Valley, Surrey, reports the case of a man, aged thirty-two, who bled profusely from a small naevus on the left forearm. There were small spots on the neck, forehead and left wrist. On several occasions he had had severe bleedings from the tumours. Dr. Bligh has kindly sent me word that there is no trace of haemophilia in the family.

[7] *Lancet*, 1907, vol. ii.

The treatment of the condition is important. At the outset it is probable that very careful cauterization of the stellate veins in the nostrils would prevent the haemorrhage. We tried this in one of our cases, and although the patient bled very profusely afterwards, losing within twenty-four hours 1,400 c.c. of blood, it seemed, however, to do good, as he had no severe epistaxis for many months. This patient had the ingenious device of a finger of a very thin rubber glove which he inserted into the nostril, and by means of a small bit of rubber tubing he blew out the finger, turned a tap and in this way successfully plugged the nostril. Calcium chloride was used in this case very freely without, I must say, any special benefit. The most successful treatment was carried out by Dr. Coe in the case reported in this paper. Certainly, the change in the patient's appearance was remarkable. Many of the spots on the face and lips had been touched with the electric wire, and, as I mentioned, the calcium lactate was given in large doses over a prolonged period. For a year he had enjoyed excellent health and had been free from bleeding. This plan of treatment should be carried out thoroughly in all the cases.

FIG. 1.

FIG. 2.

Face, and mucous membranes of mouth. Dr. Kelly's case.

FIG. 3.—Lower part of face of Mr. C.

A NOTE ON A READY METHOD OF MEASURING THE VENOUS PRESSURE WITHOUT A MANOMETER

By GEORGE OLIVER, M.D., F.R.C.P.

I HAVE observed that the venous pressure may be accurately measured without the aid of a blood-pressure instrument; a foot-rule or a measuring tape being all that is necessary. If the veins on the dorsum of the hand are sufficiently visible, it is found that when the hand is held in the vertical position with the fingers extended, and is very gradually raised, the veins at a certain height above the level of the apex of the heart are seen to collapse quite suddenly. The completion of the process is definite, for the transition from a partial to a complete collapse takes place within the space of half an inch. It is observed that the veins near the fingers collapse somewhat sooner than those near the wrist; but the difference is so slight that I prefer to take the collapse of all the veins of the dorsum as the indication for measurement. I conclude that at the moment of the collapse of the veins the blood-pressure within them is practically nil, being balanced as it were by the force of gravity; we may therefore express this force, annulling the hydrostatic rise of the blood, in millimetres of mercury. This may be done by making a very simple calculation. If we take the average specific gravity of the blood as 1·060 and that of mercury as 13·570, the 25·5 mm. contained in one inch will represent 1·985 mm. Hg. (or approximately 2 mm. Hg.). Therefore, if we multiply by 2 the number of inches above the level of the apex of the heart at which the veins collapse, we ascertain in *millimetres of mercury* the venous pressure.

This simple method of measuring the venous pressure has afforded me more uniform results than other methods, and as it enables one to discriminate between differences of 1 mm. it is definite and delicate. It is important to see that the pressure is not artificially raised. This may occur through nervous perturbation, or obstruction of the venous flow by tight clothing or even by the observer placing his hand on the forearm. The lowering effect of cold on the venous pressure should also be kept in mind.

[Q. J. M., Oct. 1907.]

A COMPRESSED-AIR HAEMOMANOMETER

By GEORGE OLIVER, M.D., F.R.C.P.

With Plate 12

I HAVE found the form of haemomanometer I am about to describe convenient and useful in clinical work. It consists of three parts—a recorder, a compressor for the regulation of air pressure, and an armlet.

The recorder (Fig. 3, A) is constructed on the well-established principle of the 'compressed-air manometer', which has been employed for many years in the measurement of the hydrostatic pressure of gases. I have found that an efficient sphygmometer merely requires the elementary mechanical components of the simplest form of the compressed-air manometer, namely, a glass tube and a liquid indicator; no additional device, such as taps or other supplementary fittings, being necessary.

The glass tube, eight or more inches in length and having a capillary bore, has a bulb at its upper end, and a smaller bulb at its lower end (Figs. 1 and 2), where it is bent up to receive a rubber tube. Just above the lower bulb, the bore is contracted (Figs. 1 and 2). The tube is mounted on a narrow strip of thin wood, through the lower end of which a pin, fixed to the sides of the box, passes; so that the tube may be raised from the horizontal position in the box to a vertical one, before and after an observation.

The indicator consists of a few drops of absolute alcohol coloured by Merck's *fett-farben Blau*—a colouring matter which does not permanently stain the glass. Should the indicator be allowed to dry up (as after prolonged disuse of the instrument) it is quickly dissolved again by adding a few drops of spirit.

The compressor (Fig. 3, B) consists of (1) a strong canvas bag, adherent to (2) two small boards (12 × 18 cm.) through which passes (3) a strong rapid screw. When in use, tap *a* is opened for the admission of air; the screw swivel *b* is unscrewed to the limit of the screw, which limit is indicated by a clicking sound; tap *a* is then closed, and the screw swivel is turned, when air is compressed into the armlet and manometer, previously connected by the rubber tubes *c* and *d*. The compressor may be used separately as in Fig. 3; or it may be set up in a box of a convenient size (namely, 9 by $2\frac{1}{4}$ by 5 inches) with the rest of the apparatus (the recorder mounted on the compressor and the standard armlet).

The armlet (Fig. 3, C) is more portable and adaptable to the shape of the limb than those now in use; and it is equally available for the forearm as for the arm. It consists of a canvas bag of the full standard width (12 by 16 cm.), to

which are attached three straps (covering the width of the bag) with friction buckles. The outer rigid cover, consisting of the straps, is, therefore, in three sections, which enable the observer to adjust the bag perfectly to the fusiform shape of the forearm.

The practical advantages of this manometric arrangement are:—

1. *The index can be read in the horizontal position*, which contributes to convenience and accuracy.

2. *The avoidance of leakage* from a defective air valve, which cannot be rectified without loss of time and trouble, and its consequence, a falling index. This not infrequent effect of the ball or pump filling, which is always an annoyance and a source of inaccuracy in observation, is entirely obviated by this valveless arrangement.

3. *The much more satisfactory control of the index* by the screw than by the pump. Another defect of ball filling is the uncertainty of regulating the compression, and thus of definitely controlling the position of the index, a certain amount of training of the co-ordination of the muscles being necessary before the observer acquires the needful dexterity. On the other hand, adaptation of the compression by means of the screw is definite and easy, even to the tiro, who, indeed, on this score has nothing to learn by practice, for he can thus graduate the position of the index, exactly as he pleases, without unintentionally overstepping or falling short of the point at which he wishes to adjust it.

4. *The gradual rise of compression* in place of the intermittent, jarring increment of it with every stroke of the pump. Needless oscillation and disturbance of the index is thus avoided.

5. *Increased precision in reading the arterial pressure* (diastolic and systolic). The compressor method of filling the armlet furnishes two grades of motion in the indicator, one or other of which can be used by the observer. When the air in the compressor, as well as that in the armlet and tubing, is in circuit, as in the ordinary use of the apparatus, the motion of the indicator is reduced to a minimum, and the reading of the arterial pressures (and especially that of the systolic pressure) then becomes much more exact than when the indicator is oscillating freely. When, however, the volume of air in circuit is reduced by closing the tap (Fig. 3, *e*) which shuts off the air in the compressor, an amplified motion of the spirit index is obtained, which the observer can thus secure, whenever he desires to do so.[1]

The objections are:—

1. The lodgement of spirit in the bore after an observation, which lodgement slightly diminishes the volume of air to be compressed; and

2. Disparity of the temperature of the air inside and outside the bore.

[1] When using the mercurial manometer I prefer the compressor and armlet to the ball filler and the ordinary armlet.

The first objection is met by raising the recorder to the vertical position for two or three minutes, when all traces of spirit will drain away from the bore, before another observation is made. The second objection is met by establishing the continuity of the air, inside and outside the bore, before each observation, as presently to be described. The observer should bear in mind that compressed-air manometers are easily affected by variations in the external temperature; he will, therefore, be on his guard, while making an observation, to avoid the play of a draught of cool air on the instrument (e.g. from a door or window), or the heating of it by the direct rays of the sun or of a fire, or by the contact of the hand.

When an observation is to be made, the observer—

1. Adjusts the armlet comfortably and *closely*;

2. Raises the recorder to the vertical position in the box, and withdraws the plug in the rubber tube attached to the nozzle.

3. He then easily disperses into the lower bulb any portion of the index which may lodge in the lower (or any) part of the bore, by taking the rubber tube, near its attachment to the recorder, between the left thumb and forefinger, nipping it so as to obliterate the bore, and then, just beyond this point, firmly nipping the tube between the right thumb and forefinger and drawing them along the tube towards its open end so as to exhaust the tube of air. On withdrawing the left thumb and finger, the spirit is quickly dislodged. The bore is thus at once sucked free from fluid, and the air within the tube, communicating with that outside, acquires the same temperature (Fig. 2). This little manœuvre is soon learnt and never fails.

4. He restores the recorder to the horizontal position, when the indicator automatically stops at the zero point (Fig. 2). Should, however, the index go slightly above the zero line, a few drops of the index fluid or spirit will restore the automatic stopping at zero.

5. He expands the compressor by unscrewing the swivel handle, closing tap *a* (Fig. 3) and making the connexions with the armlet and the indicator.

6. Finally, he compresses the air in circuit, which, on unscrewing the swivel of the compressor, may be used over and over again in a series of observations, if he desires to do so; or he may relieve the compression by unturning tap *a* (Fig. 3).[2]

[2] The apparatus is made by Mr. T. Hawksley, 357 Oxford Street, London, W.

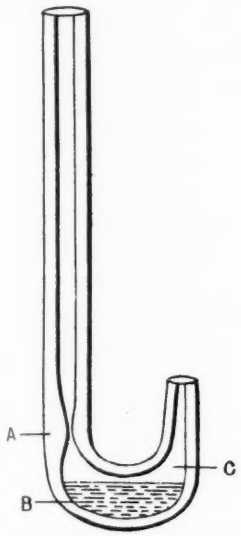

FIG. 1. Lower end of the glass tube of the indicator raised to the perpendicular position: showing A, the contraction of the bore; B, the position of the meniscus fluid; and C, the continuity of the air inside the bore with that outside.

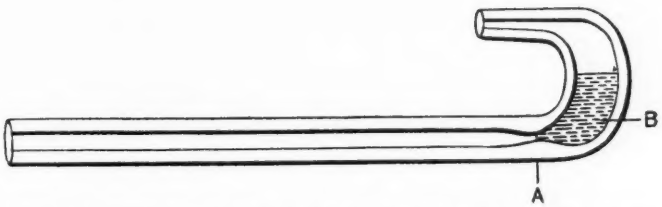

FIG. 2. Lower end of the glass tube of the indicator placed in the horizontal position ready for an observation: showing A, the zero point; and B, the position of the meniscus fluid.

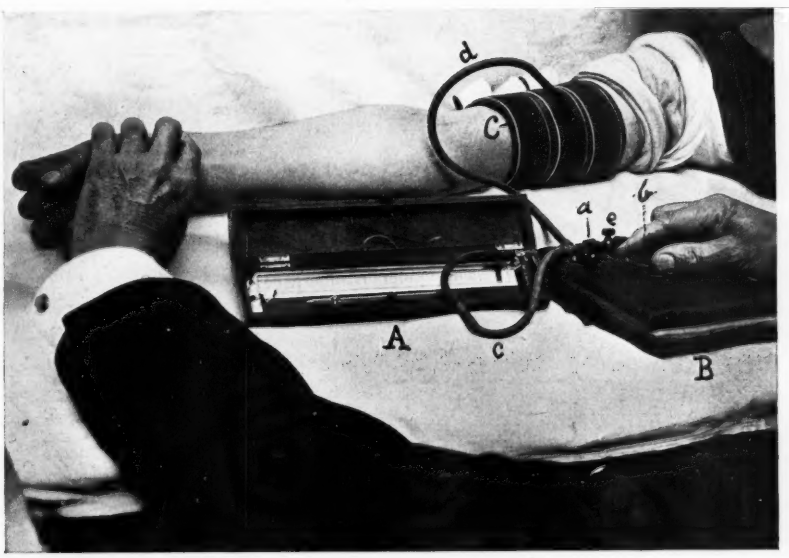

FIG. 3. The compressed-air haemomanometer. A, the recorder. B, the compressor: *a*, tap for occluding and releasing the air; *b*, swivel screw for filling the compressor and compressing the air; *c* and *d*, rubber tube connectors; *e*, tap for augmenting the oscillations of the meniscus. C, the armlet.

ON THE EXCRETION OF CREATININ AND URIC ACID IN SOME DISEASES INVOLVING THE MUSCLES

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With Plate 13

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Contents.

	PAGE
I. Introduction	63
II. Conditions of observations: Exercise. Diet	66
III. Collection and analysis of the urine	67
IV. A control observation	67
V. Variations in muscular bulk:	68
Progressive muscular dystrophy	69
VI. Variations in muscular activity:	72
A. Increase of muscular function—	72
Tetanus	72
Spastic paraplegia	76
Spastic hemiplegia	77
B. Decrease of muscular function—	78
Myasthenia gravis	78
Amyotonia congenita	81
A control	82
Locomotor ataxia	82
VII. Discussion, with table of averages:	84
(*a*) Creatinin	85
(*b*) Uric acid	86
VIII. Summary	87

I. Introduction.

The determination of the origin of the constituents of the urine is of great importance to both physiology and pathology, and a more accurate knowledge cannot fail to be of future assistance in diagnosis and treatment. Whilst the physiologist approaches this problem by observation of the normal metabolism, opportunities present themselves to the physician of supplementing the information so gained by a study of the variations accompanying disease. In some of the diseases involving the muscles the conditions are especially favourable. In the primary myopathies, for instance, the morbid process is a chronic one, and, apart from the muscular wasting, there may be no disturbance of the general health for many years. Under these circumstances, if the affected tissue is normally responsible, or mainly responsible, for any one constituent of the urine, we may expect to find this constituent excreted in diminished quantity. And, in the few observations that have been made in this class of diseases, this has usually been found to be the case.

Two of the nitrogenous bodies in the urine, creatinin and uric acid, have been associated in the literature with the metabolism of muscle.

The close relationship of creatinin to creatin, and the presence of creatin in muscle in considerable quantity, naturally led to the conclusion that creatinin was derived from muscle. This was confirmed by the findings of Rosenthal [1], Weiss [2], Langer [1], and Jakubowitsch [3], all of whom recorded a diminution of this substance in the urine in cases of muscular dystrophies. MacLeod [4], on the other hand, found no diminution. The analyses of these workers were made by the method of Neubauer—with or without Salkowski's modification—in which there is some risk of underestimating the creatinin. But although the chemical connexion between creatin and creatinin is so close, the older simple view of their relationship to one another in the body has been modified of late, for it has been found that each of them given by the mouth is excreted in the urine independently of the other [5]; to this it may be added that the balance of evidence seems to show that muscular exertion makes no difference to the amount of creatinin in the urine [6]. In view of these facts, doubts have arisen as to the direct and special connexion of creatinin with muscular metabolism; some recent writers, for instance, Gregor [7] and Van Hoogenhuyze u. Verploegh [6], concluding that it is derived from non-muscular as well as from muscular tissues; and it is clear that further evidence is required.

In the summer of 1906 the writer made estimations of the creatinin and total nitrogen in the urine upon a creatin- and creatinin-free diet in a case of pseudo-hypertrophic muscular dystrophy, which have been published in the *Biochemical Journal* [8]. The amount of creatinin excreted was less than normal, and the conclusions drawn were in accordance with the prevailing view that creatinin is specially connected with the metabolism of muscle. The diminution in the excretion of creatinin in this case, though definite, did not approach that described by earlier workers such as Weiss, who in one case found, by the Neubauer method, less than a decigramme a day in a boy of 17 with well-marked pseudo-hypertrophic muscular dystrophy.

A case of myasthenia gravis was next investigated, and estimations of the uric acid as well as of the creatinin were made. Groups of lymphocytes have been described in the muscles and viscera in many cases of this disease [9], and Dr. Golla suggested to the writer that it might be of interest to ascertain whether uric acid was excreted in excess of the normal as in

[1] Vide Langer, *Deutsch. Arch. f. Klin. Med.*, vol. xxxii, p. 395, 1883.
[2] Weiss, *Wien. Med. Wochenschr.*, 1877, p. 701; 1883, p. 613.
[3] *Neurol. Centralbl.*, 1884, p. 279.
[4] MacLeod, *Proc. Physiol. Soc. Journ. of Physiol.*, vol. xxvi, p. vii, 1900.
[5] Klercker, Hofmeister's *Beiträge*, vol. viii, p. 59, 1906. See also Folin, *Lancet*, Sept. 15, 1906, p. 738.
[6] Van Hoogenhuyze u. Verploegh, *Zeitschr. f. Physiol. Chemie*, vol. xlvi, p. 415, 1906.
[7] Gregor, *Zeitschr. f. Physiol. Chemie*, vol. xxxi, p. 98, 1900.
[8] Spriggs, *Biochemical Journ.*, vol. ii, p. 206, Feb. 1907.
[9] E. F. Buzzard, *Brain*, vol. xxviii, p. 438, 1905.

leucocytosis. This was not found to be the case. About this time a communication was made by J. B. Leathes to the Physiological Society in which the question of a relation between the excretion of uric acid and muscular tone was mooted. The fact that in the patient with myasthenia gravis, whose muscular tone was low, the excretion of uric acid was normal seemed to be against such a relation, and this suggested that some evidence as to the origin of this substance as well as of creatinin might be obtained by the examination of a number of cases of disease of the muscles.

Since uric acid was shown by Horbaczewski to be derived from nuclein bodies in the food or in the tissues, it has been generally accepted that the uric acid which is passed out upon a purin-free diet has been formed from the oxidation of the nuclein bodies of cells undergoing disintegration in the ordinary course of metabolism, and particularly from the nuclei. Burian [10] has recently questioned whether enough uric acid is formed in this way to furnish the three to six decigrammes which are passed out daily, and has put forward the view that the greater part of the endogenous uric acid is formed from purin bases which are continually being built in living muscle. In support of this he published experiments showing that muscular exercise was followed by a marked increase in the excretion of the uric acid. Previous workers had failed to obtain this increase, except with exertion so excessive as to be outside physiological limits, but this Burian ascribes to the collection of urine over too long periods. Burian's views have met with opposition from Sivén [11], who points out that the increase of uric acid observed is in part at least accounted for by the usual diurnal rise. Sivén's own experiments, in which the muscular work was done at different times in the day, showed no such effect.

The figures which Leathes recently brought before the Physiological Society showed that upon a purin-free diet the injection of strychnine, or exposure to cold, was followed by an increased excretion of uric acid, and he suggested that this was associated with an increase in muscular tone produced by these agencies.

A consideration of the above views, both in regard to creatinin and to uric acid, led the writer to undertake the series of observations here recorded in the hope of obtaining further information.

The following cases have been investigated :—

Two cases of primary muscular dystrophy [12].
Two cases of tetanus.
Two cases of muscular spasticity.
One case of amyotonia congenita.
One case of myasthenia gravis.
One case of locomotor ataxy.
Two normal cases for control.

[10] Burian, *Zeitschrift f. Physiol. Chem.*, vol. xliii, p. 532, 1905.

[11] Sivén, *Skand. Arch. f. Physiol.*, vol. xviii, p. 177, 1906.

[12] In addition to the one published in the *Biochem. Journal*, loc. cit., in which the uric acid was not estimated.

For the opportunity of observing these cases the writer is deeply indebted to the Physicians and Surgeons in charge of them, whose names are mentioned in connexion with each patient, and especially to Dr. James Collier, who very kindly interested himself in the investigation, and obtained permission for the writer to make observations upon the patients in the National Hospital for the Paralysed and Epileptic, Queen Square, where every facility was afforded by Dr. S. A. K. Wilson, the Resident Medical Officer.

II. Conditions of Observations.

In order that reliable conclusions may be drawn from such a series it is essential that the patients should be as far as possible under the same conditions of life, especially as to exercise and diet. Further, no food must be included in the dietary which might yield either creatinin or uric acid to the urine. We can then be assured that the quantities of these substances found by analysis are really derived from the tissues and not from the food, that is to say, are endogenous in origin.

As regards exercise, every patient was kept entirely in bed during the whole period of the observations.

The diet as regards its constituents was the same for every patient; it was constructed so as to contain—except in minute quantities—neither creatin nor creatinin nor purin bodies, and the following standard quantities were ordered in each case:—

Bread	12 ozs.	Eggs	8 ozs.
Butter	2 „	Jam	1 oz.
Sugar	1 „	A rice pudding.	
Cream	5 „	A cornflour blancmange.	
Milk	1 pint.	Imperial drink. Water.	

It was not, of course, possible for each patient to take the whole of this. Any variations from the standard, either in the direction of taking a smaller or greater amount, were noted, and the nitrogen content and the caloric value of the food estimated daily, as recorded in the tables. These estimates were made from published figures, and must be regarded as approximations only, and not as absolute values. The variations from day to day may be looked upon as accurate. The two cases of tetanus form exceptions, for their food was necessarily determined by the exigencies of treatment, and it was not possible to give a constant diet. In Dr. Ewart's case no purin- or creatinin-containing food was given until the sixth day after admission, and in Dr. Fawcett's case until the tenth day. In Dr. Collier's case of myasthenia gravis weak tea and coffee were allowed during a part of the experiment, as recorded in the table; their omission seemed to have no appreciable effect on the excretion of uric acid.

No drugs were given during the experimental period, except as recorded in the case of myasthenia gravis, and in the cases of tetanus, which were treated with anti-tetanic serum and other medicines.

III. Collection and Analysis of the Urine.

The urine was placed in a stoppered bottle with chloroform as soon as passed, and collected daily for the twenty-four hours from 8 a.m. to 8 a.m. Each morning it was brought to the laboratory, and usually analysed on the same day. When this was not possible the creatinin was estimated first, and the analysis of the uric acid and nitrogen commenced, and completed later. The nitrogen was determined by Kjeldahl's method, the uric acid by Hopkins' method, the ammonium urate being washed four times with saturated ammonium sulphate solution, and titrated against potassium permanganate. The washing process is facilitated by the use of Schleicher's hardened filter-papers on a pump, and this is especially the case when the quantity of uric acid in 100 c.c. of urine does not exceed 50 milligrammes. The creatinin was determined by the picric acid reaction of Jaffe[13], applied quantitatively to urine by Folin[14]. Duboscq's colorimeter was used. In those cases in which the creatinin was present in small quantities and a larger amount of urine than usual had to be taken for estimating the creatinin, it was found necessary to increase the amount of the reagents, and particularly of the picric acid, in order to get the maximum colour, but not of course in proportion to the amount of urine taken. In such cases a second estimation was made, a little more picric acid and alkali being added than had been taken with the first. If the same result was obtained the analysis was taken as correct. If not, a third quantity of urine was taken, and so on until the readings were constant.

IV. A Control Observation.

The composition of the urine is so intimately dependent upon the conditions of life, especially as to age and diet, that figures obtained from patients in bed cannot with accuracy be compared with those given for normal people under a different régime. In order therefore to obtain an adult standard, a healthy woman of twenty-one years was kept in bed upon the standard diet and the urine analysed for six days. The subject was not especially fat or lean.

For the sake of clearness, when dealing with subjects of varying weights the number of milligrammes of creatinin or uric acid passed out per kilogramme of body-weight will usually be referred to instead of the actual amounts per diem. In comparing different patients, it must be remembered that a large proportion of fat makes the amount per kilogramme appear less than it otherwise would, and vice versa. The percentage of the total nitrogen excreted in the form of creatinin or of uric acid gives another valuable means of comparison, especially when about the same amount of nitrogen is being metabolised per unit of weight, as was usually the case with these patients.

[13] Jaffe, *Zeitschr. f. Physiol. Chem.*, vol. x, p. 399.
[14] Folin, Ibid., vol. xli, p. 223, 1904.

The ratio $\frac{\text{creatinin}}{\text{uric acid}}$ gives a measure of the relation of these two bodies to one another. It may be lowered in value either by a diminution of creatinin or a rise in the uric acid, and we shall see that both of these factors come into play in one or other of the cases.

Case I. A normal woman in bed upon the standard diet.—J. M. ♀ aged 21. In St. George's Hospital, under the care of Mr. Pendlebury. The patient, a domestic servant, was admitted with an enlarged patellar bursa, and was placed upon the diet in the interval before operation. During this time the skin over the affected knee was being prepared by antiseptic compresses.

	Urine									Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
Apr 4	500	6·69	·12	·71	3·9	13	·27	1·3	5	11	2479	44	56·5	Third day of standard diet
5	910	14·16	·25	1·69	4·4	30	·57	1·4	10	10	2138	38	—	
6	780	—	—	1·07	—	—	—	—	—	—	—	—	—	Contamination with faeces
7	690	8·90	·16	·87	3·6	15	·32	1·2	6	12	2498	44	—	
8	690	10·35	·18	1·02	3·6	18	·40	1·3	7	12	2498	44	56·6	
9	750	10·88	·19	1·20	4·1	21	·41	1·2	7	12	2498	44	—	
10	690	8·70	·15	1·90	3·9	16	·30	1·2	5	12	2498	44	—	
			Averages		3·9	19		1·3	7					

The $\frac{\text{creatinin}}{\text{uric acid}}$ ratio is 2·7.

The inequality between the amount of urine and of total nitrogen on the 4th and 5th of April is evidently due to the passage of a quantity of urine on the 5th soon after 8 a.m., which should properly have been counted with that of the 4th. Every effort was made to avoid this in all the cases, the nurses instructing the patients to empty the bladder immediately before 8 a.m. each day.

The last line of the table gives the averages of the percentage of the total nitrogen excreted in the form of creatinin and uric acid, and of the milligrammes of each substance excreted per kilogramme by this patient, and may be taken as normal figures for a young adult in bed upon the standard diet. The figures are usually rather lower in women than in men; this is probably due to the greater proportion of fat in women.

V. Variations in Muscular Bulk.

Cases II and III. In both these patients the muscular tissues had undergone very great wasting, without any other obvious disturbance of health.

Case II. Progressive Muscular Dystrophy.—F. L. Male, 15¾. In the National Hospital for the Paralysed and Epileptic, Queen Square, under the care of Dr. Batten. Admitted, March 4, 1907.

Three of the patient's sisters have suffered from the same disease. Eight years ago it was noticed that the patient easily became tired. Three years later he could not get up from his chair without aid, and for the last two years he has been unable to walk properly. *At the present time* he cannot walk or stand, and is extremely lean, as is shown in the photograph in Plate 13. The muscles of the upper extremity are wasted, especially the deltoid, biceps, triceps, pectorals, the scapular muscles, and the trapezii. The infraspinati are not hypertrophied. The arm cannot be abducted or raised. The intrinsic hand muscles are normal and the grasp fair. The head can be supported. The thorax is rhachitic, the abdominal muscles unaffected. The thighs are wasted and the glutei small, but the loss of power in these muscles is greater than the apparent wasting. The calves are large and flabby. There is pes equinus with slight varus. The only reflexes that can be obtained are the superficial abdominal, and a feeble contraction of the left quadriceps on tapping the patella tendon. The tongue shows a coarse tremor. The reaction to faradic and galvanic electricity is absent or diminished in all the affected muscles. Temperature normal. Urine free from albumin and sugar.

The patient was treated with cod liver oil and malt and meat juice.

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
Apr. 9	810	9·06	·24	·64	2·6	17	·38	1·4	10	14	2843	76	37·2	Third day of standard diet
10	840	9·60	·26	·20	·8	5	·41	1·4	11	15	3111	84	—	
11	1090	10·76	·29	·23	·9	6	·42	1·3	11	14	2769	74	37·5	
12	1550	12·02	·32	·27	·8	7	·46	1·3	12	15	3111	83	—	
13	870	11·88	·31	·28	·9	7	·49	1·4	13	15	3111	82	38·1	
14	1610	13·05	·34	·25	·7	7	·44	1·1	12	15	3111	82	—	
15	1300	10·89	·29	·24	·8	6	·43	1·3	11	14	2920	77	38·1	
16	1280	11·39	·30	·25	·8	6	·44	1·3	12	15	3111	82	—	
17	—	—	—	—	—	—	—	—	—	—	—	—	—	Ordinary diet with meat
18	1080	13·85	·36	·34	·9	9	·68	1·6	18	14	2490	65	—	
19	1350	13·59	·35	·25	·7	7	·69	1·7	18	14	2490	64	38·8	
Averages, Apr. 10–16					·8	6		1·3	12					
„ on ordinary diet					·8	8		1·65	18					

The first day shows a much higher excretion of creatinin than any subsequent day. This is probably due to meat juice containing creatinin, and taken before the observations began, as the patient was being treated with that substance until the commencement of the experiment. The ordinary hospital diet containing meat did not seem to have any marked effect upon the amount of creatinin, although it was followed by a definite rise in the excretion of uric acid.

In the seven experimental days the amount of creatinin passed out was extraordinarily low, 2 to 2·8 decigrammes. The writer does not know of any recorded figures so low for a boy of this age with the exception of the cases of Weiss and Langer already mentioned, in which quantities of less than a decigramme and just over a decigramme were found by the Neubauer method, and in which the urine was not analysed on several successive days. A normal boy of 16 will pass out rather less creatinin than at a later age. Nevertheless the differences from the normal found in this case are so great that it is fair to compare the averages of these figures with those of the normal woman, aged 21.

	Creatinin		Uric Acid	
	N. % of total N.	Mg. per kg.	N. % of total N.	Mg. per kg.
Case I. Normal. J. M. ♀ 21	3·9	19	1·3	7
Case II. Myopathy. F. L. ♂ 16 . .	·8	6	1·3	12

It is impossible to avoid connecting the enormous fall in the excretion of creatinin in this case, as compared with the normal woman, with the great diminution in muscular bulk. The milligrammes of creatinin per kilogramme would be much lower had the boy been as well covered with fat as the woman, and this will explain why he passed out 12 milligrammes of uric acid per kilogramme as against 7 in Case I.

Bearing this in mind, and considering that the percentage of nitrogen passed out as uric acid is normal, we may conclude that the excretion of uric acid was unaffected by the great muscular wasting. The nitrogen metabolism per kilogramme was also rather greater than in Case I, as is seen by referring to column 4 of the table, and this again is to be attributed to the leanness of the patient.

Case III. Progressive Muscular Dystrophy.—H. V. Male, 22. In the National Hospital, Queen Square, under the care of Dr. Tooth. Admitted March 8, 1907. The patient, who is a butcher's assistant, has been thrown out of a cart three times at the ages of 14, 16, and 17. After the last accident he was unconscious for half an hour. Four and a half years ago he noticed that the thighs were wasted, and had difficulty in rising from the sitting position. A fortnight later both upper arms were affected, and he could not

easily straighten his back. He was in this hospital Aug. to Dec. 1903. *Present Condition.* A photograph of the patient will be found in Plate 13. The supraspinatus, serratus, latissimus dorsi, the upper parts of the deltoid and pectoralis, and the triceps, except the outer head, are weak and wasted. The biceps and supinator longus have practically disappeared. The lower part of the deltoid, the infraspinatus, and the outer head of the triceps are hypertrophied. The scapulae are winged. The erector spinae is weak, and there is some lordosis. The glutei, the quadriceps, and the adductors of the legs are weak. The calves are not obviously hypertrophied. There is double pes cavus. The patient turns over to rise in the characteristic way. The gait is rolling, with the feet apart and the toes out. The electrical reactions are diminished. No R. D. The triceps reflex is present, the other arm reflexes absent; knee and ankle jerks present. The tongue shows a slight tremor. The general nutrition, apart from the affection of the muscles, is good. The temperature is normal. The urine is free from albumin and sugar.

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
Apr. 11	1310	13·25	·26	·60	1·7	12	·50	1·3	10	15·3	3110	62	49·4	Fourth day of standard diet
12	950	12·73	·25	·53	1·6	11	·49	1·3	10	15·3	3110	62	50·1	
13	1080	13·00	·26	·55	1·6	11	·50	1·3	10	15·3	3110	62	—	
14	1520	12·16	·24	·55	1·7	11	·44	1·2	9	15·3	3110	63	—	
15	890	12·43	·25	·57	1·7	12	·57	1·5	12	12·1	2414	63	49·7	
16	1210	13·59	·27	·63	1·7	13	·59	1·4	12	—	—	—	—	
17	1310	13·85	·27	·41	1·1	8	·54	1·3	11	—	—	—	50·3	Ordinary diet with meat
18	1380	15·06	·30	·51	1·2	10	—	—	—	—	—	—	—	
19	1230	12·97	·26	·47	1·3	9	·55	1·4	11	—	—	—	—	
Averages on special diet					1·7	11		1·3	10					
Averages on ordinary diet					1·3	10		1·4	11					

This was a marked case of pseudo-hypertrophic muscular dystrophy, but the wasting was not advanced to such a degree as in Case II. The creatinin is excreted in a proportion much below the normal, but it is not so low as in Case II. In fact, in these two patients the excretion of creatinin and the degree of the muscular affection seem to correspond with one another.

No such relation exists between the amounts of uric acid passed out. The percentage of the total nitrogen passed out as uric acid is the same. The uric

acid per kilogramme is rather less in Case III, corresponding to his adult age and greater weight.

As in Case II, an ordinary diet with meat is followed by an increase of uric acid, but not of creatinin, indeed rather less of the latter was passed out.

VI. Variations in Muscular Activity.

A. *Increase of Muscular Function.*

The next four patients were selected as types of disease showing an increase of muscular activity, two of tetanus with excessive activity and two of chronic spastic conditions as examples of increased tone.

Case IV. Tetanus.—W. S. Male, 39. Guy's Hospital, under the care of Dr. Fawcett. Notes by Mr. C. H. Rippmann, Clinical Assistant. Admitted June 13, 1907. On May 29 the patient fell on to a piece of wood with a nail in it, which penetrated the foot. Some inflammation followed, and prevented him from working. On June 9 his jaws became stiff. On June 13 his legs were stiff for two hours from the hip to the toe, and he was brought up to the hospital, and before being got to bed was three times seized with spasm. *On admission* the mouth can be opened about ½ inch, the masseter being hard and tense. Can swallow fluids only. The abdomen and legs are rigid, the arms less so. He can get up and stand, and does so in order to micturate. The wound was at once excised, and 20 c.c. of anti-tetanic serum injected, and four hours later 50 c.c. June 15. Two short attacks in the night. Rigid. 20 c.c. of serum at 11 a.m. and 50 c.c. at 11 p.m. Took some toast and a boiled egg. Felt hungry. June 16. Back, abdomen, masseters rigid. No definite attacks, but slight exacerbations with sweating. 100 c.c. serum. Chloral hydrat. gr. 10, pot. brom. gr. 20, t. d. s. June 17. Last strong spasm to-day. June 23. Abdomen and back rigid, but much more comfortable. June 25. Last small spasm. June 30. Still a little stiff. Eating ordinary food. July 2. Abdomen rather rigid; legs, arms, and jaw normal. Left the hospital.

Urine										Food					
				Creatinin			Uric Acid					Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	C./U.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
June 14	765	12·23	·15	1·77	5·4	21	·91	2·5	11	1·9	3	400	5	85·7 (84)	Creatin-, creatinin-, and purin-free diet. 80 c.c. serum. Rigid, two attacks
15 16	1580	35·10	·21	3·34	4·3	20	1·55	1·5	9	2·2	21	2339	14	(83)	70 c.c. serum 100 c.c. Slight exacerbations
17 18	1570	38·71	·24	3·52	3·4	21	1·47	1·3	9	2·3	25	2636	16	(82)	Last strong spasm
21 22	1700	38·78	·24	3·84	3·7	24	1·84	1·6	11	2·2	23	3090	19	(81)	
23 24	1500	30·46	·19	2·72	3·3	17	1·23	1·3	8	2·1	24	3297	21	(80)	Rigid, more comfortable
25 26	2480	32·33	·20	3·06	3·5	19	1·20	1·2	8	2·4	28	3290	21	(79)	25. Last small spasm. Fish
29 30	3020	31·38	·20	2·82	3·3	18	1·34	1·4	8·5	2·1				(79)	Ordinary diet with meat. Little rigid
Averages, June 14–24					4·0	21		1·6	10	2·1		Weight after discharge = 79·8 kg.			
,, ,, 25–30					3·4	18·5		1·3	8	2·3					

This case is more complete than the following one, for the urine was all collected and an accurate account of the food kept. The diet was not the standard one; but, from the admission of the patient up to June 25, was free from purin- or creatinin-forming foods. It consisted during this time of milk, cream, blancmange, and eggs. On June 25 and 26 bread, fish, and potatoes were added.

After the first day the urine was analysed in two-day periods.

As the food was not the same the two patients with tetanus are not comparable to the rest of the series. In this case it is evident, on comparing the nitrogen in the food and the urine, that there was a considerable breakdown of protein, and nitrogenous equilibrium was at no time attained. The caloric value furnished per kilogramme per day shown in the third column from the right was also far below the minimum of 30 calories per kilogramme, which is required to support the needs of the body. The difficulty of furnishing sufficient food to an adult upon a fluid diet is always considerable, but in this disease is enormously increased. The patient could not be weighed in the course of the observations,

but his weight before and after his illness being taken, the fall in weight which took place was assumed to be as represented in brackets in the weight column, and from these figures the percentages per kilogramme were calculated.

We may here compare the excretion of creatinin and uric acid while the spasms lasted, i.e. from June 14 to 25, with the convalescent period of June 25 to 30, though in these last few days the patient was not entirely recovered, for definite rigidity of the abdomen remained; the diet also contained fish and meat, but we have seen that in Cases II and III fish and meat made no difference to the creatinin, while causing an increase in the uric acid. As in this case the uric acid is less and not more in the second period, we may take the averages as showing that more creatinin and uric acid are passed out while the spasms are occurring.

According to Senator[15] the paroxysms of tetanus cause no increase in the excretion of creatinin, and there is certainly no great increase, for the figures for the creatinin in the period of spasms are close to those of Case I, the normal woman. There seems, however, to be a definite drop in the excretion after the spasms ceased on the 23rd and 24th, when the patient became more comfortable. The highest figures, however, June 21 and 22, were not on the days of the greatest severity, but this may be due to a delayed excretion.

The uric acid as compared with Case I is raised to some extent, and the $\frac{\text{creatinin}}{\text{uric acid}}$ ratio is 2·1, as compared with the normal 2·7. This is due to a definite increase in the uric acid as compared with the creatinin. There does not appear to be any differentiation between the behaviour of the two nitrogenous bodies during and after the period of spasms. The column showing the ratio $\frac{\text{creatinin}}{\text{uric acid}}$ in the first period above the line, and the second below it, leads to the conclusion that the same proportion prevails in each period. The percentage figures in the first period are higher than they otherwise would be because of the small amount of the urinary nitrogen derived from the ingestion of food, and this is especially so on the first day.

Case V. Tetanus.—A. W. Male, 11. In St. George's Hospital, under the care of Dr. Ewart. Admitted April 29, 1907. Notes by Mr. E. H. B. Oram, House-physician. In the past two days the boy has had several spasmodic attacks, with biting of the tongue and curving of the back, and cannot now walk. On inquiry he said he had kicked his left ankle a week ago and made it bleed. *Present Condition.* Cannot open mouth properly, the masseters being firmly contracted. The head movements are limited and the abdomen rigid. Every now and then extensor spasms occur in the limbs and back, but do not produce true opisthotonus, and are not severely painful. All the muscles are hypertonic and very excitable. The deep reflexes are increased. He cannot take solid food. Temperature on admission 100° F.

100 c.c. of anti-tetanic serum were injected. April 30. Patient slept fairly under morphine (by the mouth), but woke up several times with a start, biting

[15] Vide Schäfer, *Textbook of Physiology*, vol. i, p. 600, 1898.

his tongue severely. No obvious improvement to-day. May 1. Better. Still has sudden closure of mouth. Abdomen and neck rigid. 100 c.c. of serum injected. May 4. Still improving. Urticaria has developed over chest, back, and thighs. May 15. Sent to convalescent home. A mixture containing 12 drops of Liquor Morphinae Tartratis was given on the evenings of April 29 and 30, and May 1 and 2. From April 30 6 grains of bromide of potassium were given in solution every six hours. From May 6 to 11 5 grains of calcium chloride were given every four hours.

Urine											Food				
				Creatinin			Uric Acid					Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	C./U.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
May 1	605	10·23	·40	·47	1·7	19	·49	1·6	19	1·0		Milk		circ. 25·4	100c.c. anti-tetanic serum. Spasms. Improving
2 } 3	(900)	(16·15)	—	(·85)	2·0	—	(·75)	1·6	—	1·1		Quaker oats			,, ,,
4	Lost	—	—	—	—	—	—	—	—	—		Cocoa			No spasms. Sat up. Rash
5	805	11·51	·45	·95	3·1	37	·57	1·7	22	1·7		Bread sop			E. T. 99·8 Several spasms
6	Lost	—	—	—	—	—	—	—	—	—					E. T. 99 No spasms. Fish
7	1285	10·81	·43	·67	2·3	26	·57	1·8	22	1·2					Slight spasms
8	1585	9·50	·37	·50	1·9	20	·51	1·8	20	1·0					
Averages					2·2	25		1·7	20						

Both uric acid and creatinin are excreted in greater quantity than normal for the age of the boy.

On May 5 the creatinin was remarkably high, and there were several spasms upon this day, but at the same time an urticarial rash appeared with a rise of temperature, ascribed to the antitoxic serum, and the issue is therefore not a clear one. On comparing the $\frac{\text{creatinin}}{\text{uric acid}}$ ratio, this case, like the last, does not show any clear differentiation between the creatinin and uric acid, when the early period is compared with the later, or convalescent days, with the exception of May 5, to which reference has just been made.

In the two cases of tetanus there is therefore an increase of uric acid excretion, and of the percentage of the total nitrogen passed out in this form, which is 1·6 per cent. in the man, and about the same in the boy while on a purin-, creatinin-, and creatin-free diet, a figure which is at the higher physiological limit. The creatinin is probably also increased, though not so definitely.

In tetanus the muscular contractions are so excessive that, as is well shown in Case IV, by the total nitrogen, the urine contains products of actual disinte-

gration of tissue, which cannot be regarded as resulting from normal contraction. Also the oxidation processes in the muscles are probably deficient in clinical tetanus, as in the experimental form.

It must also be remembered that the patients are under the influence of the tetanus toxin, and such an effect as an increase of uric acid might be due to an action of the poison upon protein tissues, apart from the muscular condition.

Case VI. Spastic paraplegia.—C. G. Male, 50. National Hospital, Queen Square, under the care of Dr. Ormerod. Admitted April 19, 1907. The patient had syphilis twenty-eight years ago. In August last had a carbuncle on the back of the neck. In October had an operation in St. Thomas's Hospital for perineal abscess. At this time he noticed that his legs were weak, and that he had a feeling of tightness across the lower abdomen. In the middle of December the legs became convulsed, and since then walking has been impossible. In St. Thomas's Hospital again from January 11 to middle of March. Slight incontinence of urine and faeces since November. *Present Condition.* Fairly nourished. Tongue, some tremor; protruded slightly to right. Muscles well developed. Rectus abdominis and muscles of lower extremities very rigid. Reflex spasms occasionally seen in the legs. In the intervals they are extended with marked plantar flexion of the ankles. They cannot be moved voluntarily at any joint. He cannot walk or sit up, even when assisted. Anaesthesia and analgesia almost complete below the nipples. The deep reflexes are much increased in the lower extremities, and the plantar response is extensor. Has some degree of control of the bladder, but cannot arrest micturition when once begun. Nothing abnormal made out in the spine.

The case was regarded as one of myelitis, but at the present time the possibility of compression paraplegia is being taken into account.

On admission the patient had a little pus in the urine, and this reappeared on June 23, when treatment with urotropine was resumed. On July 11 the bladder symptoms had greatly improved, an occasional condition of urgency being the only trouble. There was no incontinence. During the observations the incontinence and cystitis came on again, and for this reason the uric acid figures for the last two days are not included.

Urine											Food				
				Creatinin			Uric Acid					Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	C. $\frac{}{U}$.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
July 16	1565	10·78	·16	1·10	3·8	(16)	·42	1·3	(6)	2·7	19	3758	56	67·2	Third day of standard diet
17	1540	12·07	·18	1·21	3·7	(18)	·49	1·4	(7)	2·6	18	3615	54	67·2	
18	1415	12·41	·18	1·16	3·5	(17)					17	3579	53	67·2	
19	1040+	8·83+		(·87)	3·7						17	3579	53		
Averages					3·7			1·35		2·7					

Owing to incontinence the absolute figures are neglected in this case. The percentage of the total nitrogen excreted in the form of creatinin and of uric acid was a normal one. The $\frac{\text{creatinin}}{\text{uric acid}}$ ratio was also normal, 2·7.

Case VII. Spastic Hemiplegia. General Paralysis of the Insane.—E. C. Male, 32. Labourer. In the National Hospital, Queen Square, under the care of Dr. C. E. Beevor. Admitted March 26, 1907. The patient, who suffered from syphilis eight years ago, began to be depressed in August, 1906, and shortly afterwards complained of gradually increasing numbness in the left side. An attack followed which he describes as a sudden loss of vision for two or three seconds with severe pain all down the left side. He was taken into the Bedford Hospital, being aphasic and unable to use the left arm or leg, and remained there for six weeks. In health he can use one hand as well as the other. On returning home he was seized three times with a fit, with jerking movements of both sides, followed by temporary loss of memory and delusions. Since then has improved. *Present Condition.* Emotional. Vision each side 6/9. Argyll-Robertson pupil. Weakness of the face on the left side. The tongue deviates slightly to the left, and shows a coarse tremor. The jaw jerk is marked. Marked spasticity of the upper left extremity. Very little wasting or power of movement. Can extend and flex elbow and move shoulder; finger movements very limited. The left leg is also very spastic; there is no wasting; all movements are very limited, especially those of the distal parts. On the right side the knee jerk is increased, the ankle jerk present, and the plantar response flexor. On the left side the knee jerk is much increased, ankle clonus is present, and the plantar response extensor. In the left arm the reflexes are all increased. He has a spastic hemiplegic gait, the toes on the left side scraping the floor. The sphincters are under control. The urine is free from albumin and sugar.

Urine											Food				
				Creatinin			Uric Acid					Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	C./U.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
May 14	1945	16·10		1·87	4·3	(24)	·71	1·5	(9)	2·7	20	3967	50	78·8	Fourth day of standard diet
15	1205	12·24		1·34	4·1	(17)	·55	1·5	(7)	2·4	18	3648	46	78·8	
16	1625	14·55		1·64	4·2	(21)	·68	1·6	(9)	2·3	19	3814	48	78·8	
17 } 18 }	•														
19	1635	14·89		1·65	4·1	(21)	·73	1·6	(9)	2·3	18	3579	45	80·2	
		Averages			4·2			1·55		2·4					

In this case the percentages are again within physiological limits, although rather higher than usual. The amounts passed per kilogramme are, if no urine

was lost, normal; if there was any loss they would be higher. The $\frac{\text{creatinin}}{\text{uric acid}}$ ratio is 2·4.

It is clear then that in Case VI there is no increased excretion of either uric acid or creatinin relatively to one another.

In the second spastic case, Case VII, the uric acid is a little raised compared to the creatinin, the ratio being 2·4, and both the creatinin and the uric acid are high relatively to the total nitrogen. It is doubtful, however, whether they exceed the normal limits when we consider that the patient was a heavy man.

We may conclude that as far as these two spastic cases go they do not present definite evidence of a qualitative change in the nitrogenous metabolism. In view of the possible loss by incontinence in each case, the absolute amounts of both creatinin and uric acid excreted may, however, have been above the normal in this condition of exaggerated tone.

B. *Decrease of Muscular Function.*

The following three cases were selected as examples of the diminution of muscular function. The first is a case of myasthenia gravis, in which muscular activity was reduced to a very low level; the second a case of amyotonia congenita, in which movements could be performed, but the muscles were weak, soft, and toneless; and the third a case of locomotor ataxy.

Case VIII. Myasthenia Gravis.—E. B. ♀ St. George's Hospital, under the care of Dr. James Collier. Notes by Mr. A. W. Moore, House-physician. Admitted March 4, 1907. Twelve years ago patient was shot with a blank charge of powder, the scar from which can be seen upon the left cheek; for some weeks after this she was ill. Muscular weakness began about two years ago, when the patient fell down, and has increased since. On several occasions has seen double for a time. Has often fallen down of late, and been unable to get up without help. *Present Condition.* Well nourished. The face is expressionless and free from wrinkles, and has a sleepy appearance due to double ptosis. (See photograph, Plate 13). To look up she has to throw the head backwards. The movements of the eyes are deficient in all directions, especially upwards, even when the upper lid is supported. Pupils equal and react normally. The patient is very weak, cannot walk, and raises herself in bed with difficulty. On being asked to touch the top of her head several times in succession the movement is seen to be carried out with increasing difficulty, and before the twelfth time she is only just able to lift the arm from the bed. After a short rest she can begin again. Can only eat solid food slowly, and not much of it. Cannot talk for more than a few minutes without stopping to rest the muscles involved. The tone of the muscles is below normal. There is a small rounded tumour about the size of a cherry, which appears to be attached to the isthmus of the thyroid. Sensation normal.

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
Mar. 7	700	8·52	·17	·67	2·9		·41	1·6		12	2554	52	49·1	Third day of standard diet. Weak tea and coffee allowed
8	670	8·36	·17	·49	2·2		—	—	—	12	2554	52		E. T. 99·2°
9	—	—	—	—	—	—	—	—	—	12	2554	50	50·7	
10	890	7·52+	—	·61	3·0		·28	1·3		11	2213	44		
11	640+	6·76+	—	·47	3·9		—	—	—	12	2554	50	50·8	
12	940	10·94	·21	·76	3·9	15	·46	1·4	9	11	2443	48		1 dose H_2Cl_2 and KI
13	420+	5·36+	—	(·39)	2·7		(·25)	1·6		12	2554	50	50·8	I reaction in urine
14	550+	4·59+	—	(·33)	2·7		(·22)	1·6		12	2554	50		,, weak
15	1210	12·23	·24	·94	2·9	18	·55	1·5	11	12	2554	50	50·8	Mixture of Liq. Hydrarg. Perchlor. and KI.
16	1010	9·92	·19	·71	2·7	14	·40	1·4	8	11	2332	46		
17	910	8·90	·17	·71	3·0	14	·43	1·6	8	Sick			50·8	
18	770	—	—	—	—	—	—	—	—	12	2554	50		
19	1040	9·02	·17	·77	3·2	15	·39	1·6	7	12	2554	49	51·7	Strong I reaction in urine
20	1350	10·04	·19	·72	2·7	14	·35	1·3	7	11	2332	45		No I reaction in urine
21	1090	—	—	—	—	—	—	—	—	12	2554	49	51·9	
22	1100	9·79	·19	·73	2·8	14	·31	1·0	6	12	2554	49		
23	1070	—	—	—	—	—	—	—	—	12	2554	50	51·3	
24	920	—	—	—	—	—	—	—	—	14	2886	56		Tea & coffee omitted
25	1160	11·40	·22	·80	2·6	16	·36	1·1	7	14	2886	56	51·7	Sore throat
26	1260	13·22	·26	·73	2·1	14	·33	·8	6	11	1680	32		Aspirin, gr. 30
27	520	11·68	·23	·90	2·8	17	·48	1·4	9	10	1458	28	51·4	E. T. 102°. Fe_2Cl_6 reaction in urine
28	—	—	—	—	—	—	—	—	—	10	1458	28		M. T. 101°, E. T. 103°
29	450	10·42	·20	·81	2·9	16	·53	1·7	10	10	1458	29	50·8	M. and E. T. 100°. No Fe_2Cl_6 reaction in urine
30	570	12·25	·24	·78	2·4	15	·56	1·5	11	10	1458	29		M. and E. T. 99·4°
31	720	9·00	·18	·63	2·6	12	·48	1·8	9	10	1458	29		M. T. 99·8°, E. T. 99·4°. Patient very weak
Apr. 1	870	8·46	·17	·76	3·3	15	·56	2·2	11	11	1680	33	50·8	T. normal
Averages from March 7–22					3·0	15		1·4	8	Ratio $\frac{\text{creatinin}}{\text{uric acid}} = 1·9$				
Averages during febrile period, March 27–31					2·7	15		1·6	10	,, ,, = 1·5				
Post-febrile day, April 1					3·3	15		2·2	11					
Averages in normal Case I					3·9	19		1·3	7					

The figures per kilogramme are left out whenever there is any reason to suspect a loss of urine.

This patient was the same age and weight as the normal woman, Case I, and, except that she was allowed weak tea and coffee up to March 24, they were upon the same diet.

On comparing the figures with the averages for Case I, it is seen at once that, in the non-febrile period, the patient with myasthenia excreted less creatinin, both absolutely and relatively to the total nitrogen, than the normal woman, but practically the same amount of uric acid. The extreme depression of muscular activity and tone appears therefore to be associated with a definite diminution of the excretion of creatinin, and this is, as far as can be judged, independent of any alteration in the muscular bulk.

M. Kaufmann[16], in a series of observations upon the metabolism of a case of myasthenia, estimated the creatinin on two occasions, finding it much lower than in this case, viz. ·04 and ·06 grammes per day; the zinc chloride method was used. The uric acid nitrogen was also low, but within physiological limits. Kaufmann also recorded the presence of lactic acid in the blood. In this case Dr. Golla, using Hopkins' thiophene test, after removing protein, obtained only the same intensity of the lactic acid reaction in a measured quantity of blood from the forearm, after a series of muscular contractions, as in a control experiment upon a normal individual. In each case a dynamometer was squeezed to the 50 mark twenty times.

The administration of a mixture containing perchloride of mercury and iodide of potassium was accompanied by a definite diuretic effect with an increase on the first day in the excretion of nitrogen and creatinin. On the second day the quantities had returned to their previous level, and no effect was noticeable in the analyses upon the cessation of the medicine, or upon the disappearance of the iodine reaction from the urine two days later.

During the course of the observations the patient suffered from a sore throat, with a rise of temperature. At the onset 30 grains of aspirin were given, and as salicylic compounds have been found to cause an increase in the excretion of uric acid in the urine,[17] in order to note the effect of fever the figures for the 26th and 27th may be neglected; on the 29th the reaction for salicylates had disappeared from the urine. No effect is, however, traceable in this case from the aspirin. According to Rockwood and Epps[18] salicylates do not influence the excretion of creatinin.

Comparing the febrile with the normal period, it will be seen that the excretion of uric acid was raised during the fever, both absolutely and relatively to the total nitrogen. The creatinin is unaffected. Cario[19], in 1888, Linser and Schmidt[20], and recently Leathes[21], have found a rise of uric acid in fever. Leathes also found a less marked increase in creatinin, which is not evident in this

[16] M. Kaufmann, *Monatschr. f. Psych. u. Neurol.*, vol. xx, p. 4, 1906.
[17] J. Fawcett, *Guy's Hospital Reports*, vol. lii, p. 1112, 1895, where references will be found.
[18] Rockwood and Epps, *American Journ. of Physiol.*, vol. xix, p. 97, 1907.
[19] Vide v. Noorden, *Handb. der Pathol. des Stoffwechsels*, vol. i, p. 599, 1906.
[20] Linser and Schmidt, *Deutsch. Arch. f. Klin. Med.*, vol. lxxix, 1904.
[21] Leathes, *Journ. of Physiol.*, vol. xxxv, p. 205, 1907.

case; the febrile attack was not, however, of a severe nature, although it rendered the patient extremely weak, and on the day of the highest temperature the urine was lost. The usual febrile increase in the excretion of nitrogen is well marked.

Case IX. Amyotonia Congenita.—H. A. C. Male, 4¼. In the National Hospital, Queen Square, under the care of Dr. James Collier. Notes by Dr. Wilson. Admitted Feb. 18, 1907. The patient has always been delicate. He was a full-time child; instruments were not used. Fed at the breast. Has had measles, whooping cough, chicken pox, bronchitis, and pneumonia, and frequent coughs. Learned to speak at the usual time. In infancy the limbs were noticed to be loose. The knees and hips were flexed, and the ankles extended, so that the back of the foot touched the leg. The legs were often blue, and he was subject to chilblains. He suffered from enuresis, formerly, and from constipation. The legs were always thin. *Present Condition.* The child is small, thin and feels soft (see photograph, Plate 13). Teeth bad. Intelligence fair, and sphincters normally controlled. Some broncho-pneumonia was present on admission, but this had cleared up before the observations recorded below were made. The muscles throughout are atonic; they feel soft and velvety, and it is difficult to define their outlines when they contract. The joint structures seem equally lax, and the limbs can be put into all sorts of positions. The dorsum of the foot can be made to touch the shin, as is shown in the second photograph of this case, the gastrocnemius being stretched like elastic. Such manipulations give no pain. There is no ball to the great toe, the plantar surface being almost flat. No webbing of toes or fingers. The muscles of the arms and hands are in a similar condition. There is a kyphotic curve from the top to the bottom of the spine. The child cannot sit up unaided. The neck is thin and the head sometimes topples. He cannot stand up for more than a second, and then not straight up. All movements are weak and slow. There is also some contracture of each adductor group in the leg, with limitation of abduction and of extension at the knee. All other movements are normal in range, or exceed the normal. The reaction to faradism and to galvanism is much diminished; there is no polar change. The child can bear a strong faradic current without discomfort. The deep reflexes are absent.

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
Apr. 29	605	5·11	·41	—	—	—	·13	·9	11	7	1297	105	12·4	Third day of standard diet
30	695	8·18	·65	·07	·3	6	·26	1·1	21	8	1423	113	12·6	
May 1	705	7·20	·57	·06	·3	5	·21	1·0	17	7	1466	116	12·6	
2	645	7·91	·59	·07	·3	5	·23	1·0	17	9	1755	132	13·3	
3	—	—	—	—	—	—	—	—	—				13·3	
4	1100	13·05	·49	·05	·3	4	·48	1·2	18	7	1502	113	13·3	
5										7	1549	116	13·3	
Averages					·3	5		1·0	17	Ratio $\frac{\text{creatinin}}{\text{uric acid}} = ·3$				

It is clear that in this extremely interesting case the excretion of creatinin is low. As a child of this age cannot be compared with an adult, some analyses were made of a normal boy of the same age and a slightly greater weight, convalescent from a mastoid operation in the Victoria Hospital, under the care of Mr. Fedde Fedden. The total quantity of urine could only be collected on the second of the three days on which the urine was analysed, but the percentages on the other days will serve for comparison.

Case X. Normal boy (convalescent from mastoid operation).

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg. per day	Wt. kg.	Remarks
May 19	490+	(3·33)		(·11)	1·2		(·11)	1·1		10	1757	122	14·4	Third day of standard diet.
20	680	7·72	·53	·19	·9	13	·20	·9	14	10	1757	121	14·5	
21	580+	(5·68)		(·15)	1·0		(·15)	·9		10	1757	121	14·5	
			Averages		1·0	13 (1 day)		1·0	14 (1 day)			Ratio $\frac{\text{creatinin}}{\text{uric acid}} = ·9$		

Placing the averages together we obtain:—

	Creatinin		Uric Acid	
	N. % of total N.	Mg. per kg.	N. % of total N.	Mg. per kg.
Amyotonia congenita	·3	5	1·0	17
Convalescent boy	1·0	13 (1 day)	1·0	14 (1 day)

The boy with the lowered tone therefore passed out less than half as much creatinin as the normal boy, the uric acid remaining about the same. The control boy was much the fatter of the two, and if this be allowed for, the difference between the creatinin figures per kilogramme will be accentuated, and the uric acid per kilogramme still nearer to that of the normal boy. It is possible that the small amount of creatinin may be to some extent accounted for by a smaller bulk of muscle in the boy with amyotonia, but the diminution in bulk was not thought to be sufficient to explain the reduction of the creatinin to a third of that of the control case.

It is difficult to escape the view that this low excretion of creatinin is associated with the softness and loss of tone of the muscles, while the normal level of the uric acid is equally striking.

Case XI. Locomotor ataxy.—A. M. Female, 35. In St. George's Hospital,

under the care of Dr. Rolleston. Notes by Dr. Golla, Medical Registrar. Admitted July 15, 1906. Married seventeen years. No children. No miscarriages. History of possible venereal infection four years ago. Present illness began with an attack of herpes over the area of the eleventh and twelfth left dorsal nerves. For twelve months has had pain in the back, and for the last six months difficulty in walking. *Present Condition.* Healthy looking woman with good colour. Staggers very much in attempting to walk. Complains of a zone of pain around the lower part of the abdomen. The muscles of the lower extremities are hypotonic, and no knee or ankle jerk can be obtained. There is no muscular wasting. In the upper extremities the deep reflexes are obtained. The sense of position in the lower extremities is absent, in the upper, present. Tactile sensation is present, but the sensation to pain is lost in the lower extremities and trunk, and the major part of the arms. The sense of muscle pain is lost in both arms and legs. In the tongue the sense of pain is lost, that of touch preserved. Argyll-Robertson pupil. Sphincters unaffected.

Urine										Food				
				Creatinin			Uric Acid				Calories			
Date	Quantity of urine c.c.	N. in urine	N. per kg.	G. per day	N. as % of total N.	Mg. per kg.	G. per day	N. as % of total N.	Mg. per kg.	N. in food	per day	per kg per day	Wt. kg.	Remarks
July 18	445+	(5·89)		(·50)	3·1		(·24)	1·3		12	2485	54	46·0	Third day of standard diet.
19	760	12·50	·27	1·04	3·1	23	·41	1·1	9	12	2485	54	46·1	
20	835	10·80	·23	·86	3·0	19	·34	1·0	7	12	2411	52	46·3	
21	1245	13·00	·28	1·00	2·8	22	·43	1·1	9	12	2485	54	46·3	
Averages					3·0	21		1·1	8	Ratio $\frac{\text{creatinin}}{\text{uric acid}} = 2·6$				
Averages in normal Case I					3·9	19		1·3	7	Ratio $\frac{\text{creatinin}}{\text{uric acid}} = 2·7$				

In this case the amount of both uric acid and creatinin excreted per kilogramme is normal. The lower percentage of nitrogen excreted as creatinin, as compared with Case I, is due to the fact that the patient was metabolising much more nitrogen, as is seen by comparing the fourth column in this table with that on page 68. The figures for the total nitrogen when compared with the intake of nitrogen make it probable that no urine was lost on the 19th, 20th, and 21st. Hence, in this woman, the loss of tone associated with locomotor ataxy does not appear to be associated with any alteration of the excretion of the uric acid. Neither is the creatinin affected. This is of great interest in view of the small amount of creatinin passed out in the case of amyotonia congenita. It must be remembered that in locomotor ataxy the muscles are not interfered with except through the sensory path. The anterior horn cells and the motor nerves and muscles are intact. On the other hand, it is probable

that in amyotonia congenita, the seat of the affection is on the motor side, in the muscles, or at all events in some part of the neuro-muscular apparatus governed by the anterior horn cell. Just as we know that a gross lesion in this path leads to the reaction of degeneration and death of the muscle cell, so a lesser abnormality here might interfere fundamentally with the metabolism of the muscle. And at the post mortem examination of a case regarded as one of amyotonia recorded by Spiller [22], the muscles were flabby and hyaloid to the naked eye, and the microscopic appearances suggested imperfect development; the central nervous system and the peripheral nerves were found to be normal. It is possible that further light might be shed upon the problem by an extension of the chemical method of inquiry to other diseases involving the neuro-muscular apparatus.

VII. Discussion.

In the following table the average figures obtained from each case are put together in order. The figures for creatinin from the previously published case of pseudo-hypertrophic muscular dystrophy are inserted between the averages of Cases II and III.

Table of Averages.

Case	Disease	Reference	Age	Weight kilog.	Creatinin		Uric Acid		Ratio Creatinin / Uric Acid
					N. as % of total N.	Mg. per kilo.	N. as % of total N.	Mg. per kilo.	
I	Healthy . . .	p. 68	21	56	3·9	19	1·3	7	2·7
II.	Myopathy . .	p. 69	16	38	·8	6	1·3	12	·5
	„ (*Biochem. Journ.*) .	[23]	29	50	1·2	10	—	—	
III.	„ . . .	p. 71	22	50	1·7	11	1·3	10	1·1
IV.	Tetanus . . .	p. 73	39	82	4·0	21	1·6	10	2·1
V.	„ . . .	p. 75	11	25	2·2	25	1·7	20	1·1
VI.	Spastic paraplegia .	p. 76	50	67	3·7	—	1·3	—	2·7
VII.	Spastic hemiplegia .	p. 77	32	79	4·2	—	1·5	—	2·4
VIII.	Myasthenia . . .	p. 79	22	51	3·0	15	1·4	8	1·9
	„ Febrile period	p. 79			2·7	15	1·6	10	1·5
IX.	Amyotonia congenita	p. 81	4	13	·3	5	1·0	17	·3
X.	Healthy boy . . .	p. 82	4	14	1·0	13	1·0	14	·9
XI.	Locomotor ataxy .	p. 83	35	46	3·9	19	1·3	7	2·6

[22] Spiller, *Univ. of Penn. Medical Bulletin*, xvii. 1905.

[23] loc. cit.

(*a*) *The Creatinin.*

The amount of creatinin passed out in the urine is below the normal in the primary myopathies, in amyotonia congenita, and in myasthenia gravis.

In the myopathies the excretion of creatinin is definitely related to the degree of the muscular affection, reaching a very low figure in the most severe case, that is in Case II. The amount in the urine, therefore, appears to be proportional to the bulk of normal muscle in the body[24]. This is in accordance with the isolated analyses of previous workers referred to in the introduction (p. 64), except MacLeod, and establishes the conclusion drawn by the writer in his previous paper, 'that creatinin is derived from muscular tissues to a greater degree than from other protein tissues.'

But in view of the very small quantity of creatinin found in Case II, ·2 to ·28 grammes per day, the question at once suggests itself as to whether it is not legitimate to go further and to say that it is probable that muscle is the only source of the endogenous urinary creatinin in an adult. Strictly speaking, this cannot be proved, nevertheless when we take note of the fact that in Case II the excretion is reduced to a third of the normal, and that although the patient was bedridden, a considerable amount of functionating muscular tissue must have remained to enable the vital functions to be carried on, we are led to believe that probably the still active muscle would account for the major part of the creatinin excreted. And if this be so there is very little left to be derived from any other source.

In myasthenia gravis the capacity of the muscles to contract is profoundly interfered with in some way not yet understood. The bulk of the muscles is not affected. The diminution of the excretion of creatinin is here not great, but is of importance as it appears to indicate a connexion between the excretion of creatinin and muscular function apart from bulk.

Amyotonia congenita is another obscure affection. In this case the excretion of creatinin is reduced to a third of that of a normal boy used as a control, and this again seems to connect creatinin not only with the bulk of muscle, but also with the normal development of muscular function. Loss of muscular tone by interference with the sensory path, as in locomotor ataxy, does not appear, in the case examined, to have had any effect upon the excretion of creatinin.

When we come to consider the cases of tetanus and of spastic paraplegia and hemiplegia, we find only a slight increase in the excretion of creatinin, or where, as in Case VII of spastic paraplegia, it is possible that there was a definite increase, it is not comparable in degree to the diminution found in the cases we have just been discussing.

Creatinin, therefore, is excreted in smaller quantity than the normal when the bulk of the muscular tissue is diminished, as in the myopathies; also when muscular activity and muscular tone are depressed by a pathological condition

[24] It is interesting to note that in 1869 Hoffmann (*Virchow's Archiv*, vol. xlviii, 1869) noticed that the excretion of creatinin bore a certain relation to the body-mass.

of the muscle or motor apparatus, as in myasthenia gravis and amyotonia congenita. It is unaffected when the muscular tone is lowered by an interference with the sensory path, as in locomotor ataxy. Other workers have failed to show that it is definitely affected by normal muscular contraction, and even in the abnormal activity of tetanus, and of spasticity, the increase in its excretion is slight.

It appears, therefore, probable that the creatinin is connected with the nutritional metabolism of the muscle fibre, and is not a substance formed in the act of contraction. If we liken the muscles to a machine, creatinin, as a waste product, would stand in relation to the structure of the machine, and not to the fuel which the machine uses.

(*b*) *The Uric Acid.*

The arguments which we have used in observing the creatinin may be applied in a negative sense to the uric acid. In the muscular dystrophies we see that a great diminution of muscular bulk may occur without appreciably affecting the excretion of uric acid.

In Case IV, of tetanus, the uric acid is increased in proportion to the total nitrogen and to the creatinin, as is seen by the $\frac{\text{creatinin}}{\text{uric acid}}$ ratio in column 11, page 73. It is also, relatively to the total nitrogen, in rather higher proportion in Case VII, of spastic hemiplegia, as compared with the normal woman. The patient was, however, a big man. This reminds us of Leathes' observation that the increase of muscular tone brought about by the injection of strychnine, or exposure to cold, is accompanied by an increased excretion of uric acid. But an association between an increase of muscular tone or activity and excretion of uric acid, although it suggests that the uric acid may be derived from the muscle, does not establish it; and in view of the constancy of the uric acid in Cases II and III, in spite of the enormous loss of muscular tissue, it appears probable that muscle cannot be an important source of uric acid, and that some other interpretation must be put upon Leathes' interesting experiments. This view is supported by a consideration of the cases of myasthenia gravis, amyotonia congenita, and locomotor ataxy. In spite of the lessened activity in myasthenia, which was accompanied by a depression of tone of the muscles, and of the lessening of the tone in locomotor ataxy, and of its absence in amyotonia, the excretion of uric acid is not materially affected, although the excretion of creatinin, except in the case of locomotor ataxy, was definitely lowered.

These results are opposed to the view of Burian, who has expressed the opinion, as we have seen, that the greater part of this substance is derived from muscle.

It is obvious that, under the conditions of these observations, the quantity of endogenous uric acid derived from muscle must be small, and that the uric acid in the urine is, in the main, unconnected with muscular metabolism, and should be looked upon as a visceral product.

VIII. Summary.

In two cases of primary muscular dystrophy the amount of creatinin in the urine was small, and the diminution was proportional to the muscular wasting.

In a case of amyotonia congenita the excretion of creatinin was also low, in one of myasthenia gravis it was diminished in lesser degree, and in one of locomotor ataxy not at all.

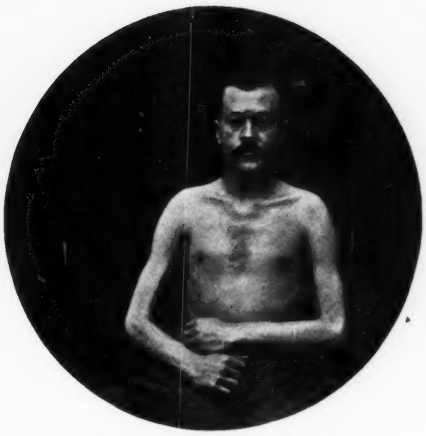
In two cases of tetanus and one of spastic hemiplegia in a general paralytic, there appeared to be only a slight increase. In a case of spastic paraplegia the excretion was normal.

In all these cases the excretion of uric acid deviated but little from the normal, being highest in the cases of tetanus and of spastic hemiplegia.

In the case of myasthenia gravis, the uric acid was excreted in greater quantity during a mild attack of fever, both absolutely and relatively to the total nitrogen.

The conclusions are drawn, (1) that by far the greater part, if not all, of the endogenous creatinin in the urine is derived from muscular tissue, but that it is a product of the internal structural metabolism of muscle, and not of its contraction, and (2) that the source of by far the greater part of the endogenous uric acid in the urine is to be looked for in the non-muscular tissues.

Case II. Photograph by Dr. Hall.



Case III. Photograph by Dr. Hall.

Case VIII. Photograph by Mr. Harris.

Case IX (1). Photograph by Dr. Wilson.

Case IX (2). Photograph by Dr. Wilson.

LEUKANAEMIA: ITS RELATION TO LEUKAEMIA AND PERNICIOUS ANAEMIA

By J. H. DRYSDALE, M.D., F.R.C.P.

The term leukanaemia was coined by Leube[1] to designate a group of cases which he thought could not be properly classified either under the head of leukaemia or pernicious anaemia. He says, 'in this form of blood disease the production of both red and white cells is thrown into disorder, and accordingly in the blood picture marked changes appear in the leucocytes as well as in the erythrocytes, such changes as we are accustomed to note in the one case in leukaemia and in the other in pernicious anaemia. Blood formation may cease entirely, and this deficiency can no longer be compensated for in any manner, so that the organism soon succumbs to the pernicious blood disease.' This group 'is distinct, in spite of the fact that not only normoblasts but occasionally megaloblasts as well are found in typical leukaemias, and conversely that a few myelocytes are often found in severe anaemias'. 'The name can only be applied when both leucocytes and erythrocytes are uniformly and decidedly damaged in their development, when the case can neither be put in the category of leukaemia or pernicious anaemia.'

The conclusions embodied in this statement he based on a case under his own charge. The patient, a boy aged 10, though always weak, had never suffered from any serious illness, and had attended school regularly up to April 22, 1900. On that date he was out of sorts and vomited twice, so that he remained at home till the 29th. On the 29th he sang, as a choir-boy, in church, and on May 1 returned to school. On May 5 he was sent home by his teacher on account of his pallor. On May 6 epistaxis occurred with yellow discoloration of the skin, and he complained of toothache, pain in the neck and epigastrium. In the course of the day he became gradually more and more apathetic, and finally comatose, and was brought to the hospital in an unconscious condition.

On admission, the patient presented all the appearances of severe anaemia. There was marked oedema of the hands and eyelids. The urine contained a trace of albumin, but no blood or casts. The liver and spleen were moderately enlarged, hard, and sensitive to pressure. There was extreme tenderness to pressure on the sternum and both femora. Ophthalmoscopic examination revealed a marantic thrombosis of the arteria centralis retinae with numerous haemorrhages. T. 102–104° F.

[1] Leube, *Deutsch. Klinik*, 1902, no. 42. See also Arenth, *Deutsch. Arch. für klin. Med.*, 1901, vol. lxix, p. 331.

[Q. J. M., Oct. 1907.]

The blood count showed only 256,000 red cells per c.mm. The corpuscles varied greatly in size, shape, and staining reaction, and there were 76 normoblasts and 152 megaloblasts per c.mm. Although the haemoglobin was not more than 10 per cent. of the normal, the colour index approached 2. The number of leucocytes was only slightly above normal, 10,600. Notwithstanding this the blood picture resembled that of leukaemia. The proportion of the various forms present, and many of the individual cells in each variety, varied greatly from the normal.

The differential leucocyte count, May 8, showed:

		%
Polymorphonuclears	4,603 per c.mm. or	43·9
Neutrophile myelocytes	1,380 „ „ „	13
Eosinophiles	25 „ „ „	·2
Eosinophile myelocytes	76 „ „ „	·6
Small lymphocytes	4,260 „ „ „	35·3
Large lymphocytes	517 „ „ „	4·9
Large mononuclears	228 „ „ „	2·1

No mast cells, or only a few poor specimens, were found after the most careful search.

For May 9 no count of absolute numbers was made, but the differential count was:

	%
Polymorphonuclears (neutrophiles)	53
Neutrophile myelocytes	15·1
Eosinophiles	·3
Eosinophile myelocytes	·5
Small lymphocytes	22·9
Large lymphocytes	5·8
Large mononuclears	2·4

In the absence of any knowledge of the absolute numbers, the variation in percentage is no help in deciding which of the varieties have increased or decreased. Of the polymorphonuclears many, even in the specimens stained by Ehrlich's triacid method, showed no granules. Intermediate forms in all stages, from cells completely granule-free to those with the normal density of granulation, were common. More than 25 per cent. of the polymorphonuclear cells were granule-free, as were nearly 29 per cent. of the neutrophile myelocytes. There was obviously some difficulty in distinguishing non-granular myelocytes from large mononuclears and large lymphocytes, but Arenth, who performed the blood examination, by a display of some ingenuity arrived at a result which was almost certainly approximately correct.

The downward course of the affection, during the four days in which the patient was in the hospital, was extraordinarily rapid. The temperature, which remained between 102·2° F. and 104° F. on the first and second days, dropped on the third to 100·4°, and on the fourth, when death occurred, to 98°. Consciousness, which had been lost before his admission to the hospital, returned and remained

to the end. Death occurred on May 9, with increasing asthenia, the heart becoming more and more dilated.

The post-mortem examination showed extreme anaemia of the entire body. Siderosis was completely absent, both macro- and microscopically. The lower half of the femur was uniformly red. The spleen only slightly enlarged, $5\frac{3}{4} \times 3\frac{1}{4} \times 1\frac{1}{2}$ inches; on section the consistence was soft, the colour paler than natural, the Malpighian tufts enlarged but indistinct. The liver was firm, and gave a faint amyloid reaction. There was no enlargement or change in the lymph glands.

Microscopically the bone-marrow contained a preponderance of large myelocytes, many with but few granules, some quite granule-free. Normoblasts were more numerous than megaloblasts. In the spleen the Malpighian bodies had undergone myeloid transformation. In the liver the capillaries contained myelocytes, and in addition there were a number of small foci of polymorphonuclear leucocytes arranged, some inside, some around the acini. No organisms could be demonstrated in these foci microscopically.

The outstanding features are, therefore, a very severe anaemia of the pernicious type; a leucocyte count hardly above normal, but showing marked changes when the differential is examined; a slightly enlarged spleen; a tendency to haemorrhages, and a rapidly fatal course. Post-mortem, a myeloid transformation of the bone-marrow, spleen, and liver, with an absence of siderosis.

A case very closely resembling this, except for a considerable increase in the number of leucocytes, has been recently under the writer's care in St. Bartholomew's Hospital.

M. W., housewife, 35, was admitted January 23, 1907, complaining of weakness and shortness of breath.

History of present condition.—She had always looked pale, but was in her usual health and able to do her work up to the time of her last confinement, on September 17, 1906. The labour was natural; there was no unusual loss of blood. She remained in bed fourteen days. On getting up she noticed herself short of breath on any exertion and easily tired, so as not to be able to do her housework. She, however, suckled her infant for $3\frac{1}{2}$ months, which was quite strong and healthy. From the time of her getting up she had got steadily worse. There was no history of haematemesis, melaena, or bleeding from the gums or elsewhere.

Previous history.—The patient had measles as a child; there was no history of other serious illness.

Family history.—Father, mother, 8 brothers and sisters were all alive and well.

On admission. She was very pale, with a yellow waxy look. There was marked pallor of the mucous membranes and elsewhere. There were several decayed teeth, and the breath was foul. The gums and throat (tonsils, &c.) were natural, apart from pallor. A swelling was found beneath the angle of jaw on the left side; she complained of toothache on that side. No glandular enlargement was found elsewhere in the neck.

Chest.—The lungs were natural. The heart area of cardiac dullness, slightly enlarged to the right. A systolic murmur was heard at the apex, not conducted widely. A systolic murmur also was present over the pulmonary area.

Abdomen.—Flaccid. The spleen could be felt 1½ inches below the costal margin; the liver 1 inch below costal margin in the right nipple line.

Some slightly enlarged glands smaller than marbles were present in each axilla.

One small haemorrhage was seen in the fundus of the right eye.

Temperature on admission, 101°. P. 140. R. 28.

Reds, 985,000. Haemoglobin, 24 per cent. Colour index, 1·2. Whites, 55,000.

Jan. 28. Reds, 884,000. Haemoglobin, 22 per cent. Colour index, 1·2. Whites, 74,000.[1]

Jan. 30. The spleen was 2 inches below costal margin; the patient was very restless; air hunger was present. The temperature remained high.

Jan. 31. The patient complained of a sense of oppression beneath the lower end of the sternum. Air hunger was marked. The spleen was 2½ inches below the costal margin. The glands in the left groin were slightly enlarged. No haemorrhages except in eye were seen. The throat and gums were natural. No tenderness or swelling of bones was found.

Reds, 588,000. Haemoglobin, 18 per cent. Colour index, 1·5. Whites, 89,700.[2]

The temperature was still high. The patient complained of great dryness of the mouth, with thirst. The respirations became more frequent. Two pints of saline fluid were injected under the skin, and for a time the patient felt better.

Feb. 1. Condition as before transfusion. In the afternoon, patient had a brisk epistaxis. The respiratory difficulty increased, and the patient died nine days after entering the hospital.

The temperature, which was 101° on admission, fell next day to normal, but rose again and remained constantly about 101°–102° till death.

Cultures made after death from the blood and bone-marrow remained sterile.

Jan. 24. Reds, 985,000. Haemoglobin, 24 per cent. Colour index, 1·2. Whites, 55,000.

[1] Differential (Jan. 28):

	per c.mm.	%
Polymorphonuclears	12,950	17·5
Large mononuclears	40,330	54·5
Small lymphocytes	5,180	7
Neutrophile myelocytes	14,800	20
Eosinophile (some myelocytes)	740	1

Careful search revealed one or two basophiles.

Normoblasts, 370; megaloblasts, 2,200 per c.mm.

[2] Differential (Jan. 31):

	per c.mm.	%.
Polymorphonuclears	11,302	12·6
Large mononuclears	41,800	46·6
Small lymphocytes	10,036	11·3
Neutrophile myelocytes	22,963	25
No eosinophiles were seen in making count, but few were found on a prolonged search.		
Basophiles	3,229	3·6

Normoblasts, 2,400; megaloblasts, 1,500 per c.mm.

Much poikilocytosis and polychromatophilia. Many dwarf polymorphonuclears; much irregularity and departure from type in all forms.

In specimens stained with eosin and methylene blue (Leishman) it was found to be a matter of extreme difficulty to make a satisfactory differential count. The reason for this was seen at once on examining a triacid specimen. In addition to the typical non-granular large mononuclear cells and finely granular myelocytes, a very large number of cells, forming a complete intermediate series between these two forms, was present. Often the granules were at the same time scanty and ill-stained, so that even with the triacid staining their classification was a matter of some doubt.

At the post-mortem examination the whole body was extremely anaemic. The spleen was considerably enlarged, very soft, and on section pale dirty brown in colour, the naked-eye structure being blurred. The glands in the left groin, mesentery, hilum of the liver, and both axillae were slightly enlarged and rather soft and reddish. The liver was slightly enlarged, pale, and firm. A longitudinal section of one of the tibiae showed the pyoid appearance typical of some cases of leukaemia.

Microscopical examination of bone-marrow smears revealed a preponderance of finely granular (neutrophile) cells, only a few of which were polymorphonuclears. In many of the cells the granules were scanty. In addition there was a considerable number of cells which could only be classed as large mononuclears, and between these and the last-named cells a continuous series could be traced. A fair number of eosinophile myelocytes and one or two basophiles were found. Nucleated reds, both normoblasts and megaloblasts, were scanty.

In the liver the vessels contained a very great excess of leucocytes, some of them non-granular large mononuclears, the majority, however, containing fine granules; polymorphonuclear cells were scanty; eosinophile cells and nucleated reds were absent.

Spleen.—A considerable increase in the large mononuclears and the finely granular myelocytes was present throughout the pulp, and in the Malpighian bodies which were not well marked off from the pulp. Nucleated reds were scanty.

Kidneys.—Hardly any change was noticeable.

The iron reaction (siderosis) was entirely absent.

An abstract of other cases published under this title is given here.

Luce[3]. Female, aged 40.

Admitted, Feb. 4, 1902. On Feb. 3 seized with malaise, fever, sore throat. Diphtheria bacilli not found. Sore throat disappeared. Feb. 13, Hb. 65%. Feb. 27, glands in neck slightly enlarged, Hb. 45%. March 7, slight increase of large mononuclears. March 26, mouth sore, gums swollen, spleen not enlarged. Reds, 2,428,000; Hb. 35%; Whites, 37,600. April 11, numerous petechiae; Reds, 1,652,000; Hb. 35%; Whites, 81,600; most of the leucocytes large mononuclears. June 16, Reds, 1,236,000; Hb. 30%; Whites, 52,600. Polymorphonuclears, 46%; myelocytes, 0·4%; large lymphocytes, transitionals, and large mononuclears, 49·5%; lymphocytes, 3·8%; eosinophiles, 3%. Many megalocytes; nearly

[3] Luce, *Deutsch. Arch. für klin. Med.*, 1903, vol. lxxvii, p. 215.

one per cent of the reds were megaloblasts and normoblasts. July 1, gland at right angle of jaw as large as a walnut. Spleen enlarged two fingers' breadth below ribs. Died, July 19.

Post-mortem. Except the glands in the neck, no glandular swelling. Lymphatic tissue of the stomach, intestine, throat and base of tongue natural. Spleen, 36 ozs. soft light-brown on section, follicles not visible. Liver, 75 ozs. Wide-spread red transformation of the bone-marrow.

Microscopically. Spleen and gland in smears, nearly all cells large mononuclear, no granular ones. Liver, a similar appearance with, in addition, some polymorphonuclears, no neutrophile myelocytes. Bone-marrow, 86 % of the leucocytes non-granular mononuclears, only 1·7 % of neutrophile and eosinophile myelocytes. 75 % of the nucleated reds megaloblasts. Siderosis entirely absent.

Hirschfeld.[4] Male, aged 19. No previous illness.

Admitted, Dec. 11, 1905. For four months before had been treated without result for 'rheumatism'. Pain in left shoulder and spine. Feb. 14, 1906, spleen felt. On March 9 blood examined for first time and showed a large increase in the number of whites, most of them 'lymphocytes' large, small and intermediate. Poikilocytosis, polychromatophilia, an occasional nucleated red, no myelocytes.

	Reds	Hb.	Whites	Polymorphonuclears	Eosinophiles	Myelocytes	Lymphocytes
March 13	1,250,000	25%	34,000	37%	8%	0%	55
March 26	1,200,000		31,000	40%	3%	5%	52
April 5	850,000		34,000	8·7%	0	3%	89, nearly all large

On March 26 complete blood picture of pernicious anaemia; on April 5 the same, but extreme. Died, April 6.

Post-mortem. Bone-marrow as in pernicious anaemia, but in addition many lymphomata. Glands very slightly swollen. The liver, kidneys, testicles, besides the bone-marrow, contained numerous lymphomata composed of large and small lymphocytes, the former predominating. In the liver myelocytes, eosinophile cells, and nucleated reds were present here and there. In the spleen here and there myeloid transformation. In the glands well-marked myeloid transformation.

Diagnosis. Lymphatic leukaemia of myelogenous origin with anaemia; secondary myeloid transformation of the glands, spleen, liver, i. e. true mixed leukaemia.

Körmöczi.[5] Female, aged 50. No previous illness.

April 23. On admission had been ill one month. Well nourished. The whole body covered with old and recent petechiae.

[4] Hirschfeld, H., *Fol. haem.*, 1906, p. 332.

[5] Körmöczi, *Deutsch. med. Wochenschr.*, 1899, No. 15, p. 238.

Gingivitis. Spleen not enlarged. Temperature 102°. No parasites or ova found in stools. May 3, very severe epistaxis. Whites, 6,000; Reds, 2,000,000; Hb. 30%; C.I., ·75. Poikilocytosis. Micro- and megalocytes. Megaloblasts. Majority of whites, polynuclears.

Date	Reds	Whites	
April 23	2,300,000	6,000	
April 30	2,000,000	6,000	On the last two days of life, when the leucocyte count was high, 95% of the cells were mononuclear. Polymorphonuclears and eosinophiles forming only 5%
May 8	1,700,000	6,000	
May 13	1,600,000	107,000	
May 14	1,600,000	107,000	

Died, May 14. Post-mortem. No siderosis. Patches of red transformation in the marrow. Microscopically preponderance of large mononuclear cells with finely granular protoplasm and very irregular outlines. Nucleated reds present. Polynuclear cells absent. Diagnosis: acute leukaemia.

Mattirolo.[6] Male, aged 9. Always in good health till the beginning of Feb. 1905, then feebleness and bleeding from the gums noticed.

On admission waxy pale, scattered petechiae in the skin. Glands in the neck, axillae, and groins hard, painless. Tonsils large with gangrenous points. Spleen and liver not enlarged. Diaphyses of bones tender. Whites, 76,000; Reds, 90,000; Hb. 20%; C.I., high. Poikilocytosis, anisocytosis, many normoblasts, very many megaloblasts. Lymphocytes 51%. Numerous neutrophile myelocytes and transitional forms. Eosinophiles scanty.

Post-mortem. Numerous cutaneous and serous haemorrhages. General hyperplasia of the lymphatic system (glands, Peyer's patches). Spleen slightly enlarged. Liver not enlarged. Red, megaloblastic, degeneration of the marrow. Large and small lymphocytes numerous. Neutrophile myelocytes less common. Microscopically the spleen and gland pulp were stuffed with lymphocytes.

Diagnosis: 'Leukanaemia'. Pernicious anaemia with acute lymphatic leukaemia superimposed.

Teeter[7] has published, under the title 'Recovery from Leukanaemia', the case of a child of six, in whom in the course of an illness characterized by malaise, vomiting, and haematuria the blood picture was that of 'leukanaemia'. After a short illness convalescence was rapid.

Zevi[8] has described a similar condition in a patient with malaria. The patient left the hospital 'cured' in a fortnight.

Kerschensteiner.[9] Whites, 56,000; Reds, 800,000; Hb. 16–18%. Polymor-

[6] Mattirolo, *Fol. haem.*, 1905, p. 395.
[7] Teeter, *Journ. Amer. Med. Association*, 1907, p. 608.
[8] Zevi, *referat Fol. haem.*, 1905, p. 695.
[9] Kerschensteiner, *Münch. med. Wochenschr.*, 1905, no. 21; *referat Fol. haem.*, 1905, p. 697.

phonuclears 77%; myelocytes 8%; lymphocytes 5–10%; large mononuclears 4–7%; eosinophiles 0·3–1%. Poikilocytosis, numerous erythroblasts, no mast cells.

Post-mortem. No myeloid transformation of liver. Myelocytic and erythroblastic changes in the spleen. In smears some eosinophile myelocytes, large mononuclears, and isolated mast cells. In the bone-marrow many normoblasts, occasional megaloblasts, many myelocytes neutrophile and eosinophile, few large mononuclears.

Weber.[10] Male, 56. Fair health till twelve months before.

Admitted, Dec. 10, 1903, for anaemia and weakness. Very great enlargement of the liver and spleen. Some oedema of the legs. Slight fever for first few days. Died, Jan. 15, 1904, from asthenia with increasing oedema. Whites, 3,000; Reds, 1,800,000; Hb. 27%. Poikilocytosis, twenty-four normoblasts, four megaloblasts, and two microblasts seen in counting 400 leucocytes.

	%
Polymorphonuclears	37·5
Neutrophile myelocytes	3·0
Eosinophiles	0·5
Eosinophile myelocytes	·0
Large lymphocytes	9·6
Small lymphocytes	49·6

The day before death Reds, 1,200,000; Hb. 25%; Whites, 12,000.

Post-mortem. Red transformation of bone-marrow. Microscopically connective tissue greatly increased, fat absent. Myelocytes and large mononuclear cells. Erythroblasts abundant. Liver uniformly enlarged, 88 ozs. Microscopically the columns of cells were separated by clumps of cells composed of myelocytes, large mononuclear cells and erythroblasts; a few scattered eosinophiles. Spleen, 66 ozs. Malpighian corpuscles natural; the pulp was permeated with cells similar to those found in the liver. Ordinary lymphatic glands not enlarged. Prevertebral haemolymph glands greatly enlarged. Siderosis entirely absent. Diagnosis: Leukanaemia, a combination of pernicious anaemia and 'pseudo-leukaemia' of the 'mixed cell' type.

Bushnell.[11] Male, aged 25. Yellow colour since three days old. Often had attacks of pain in the upper part of the abdomen and grey stools. Had 'rheumatism'. Suffered from frequent attacks of epistaxis. Noticed a lump in his belly ten years ago which had got bigger. The spleen filled the left side of the abdomen. Liver enlarged. Inguinal glands slightly enlarged. No hair on pubes or face; testes small.

Date	Whites	Reds	Hb. %	Polymorphonuclears	Eosinophiles	Myelocytes	Small Lymphocytes	Large Lymphocytes	Mast Cells	Intermediate Cells
May 6	11,000	1,120,000	15	60·8%	1·2%	1·6%	23·1%	6·5%	0·6%	4·6%
June 3	2,400	1,280,000	25	64·8%	3·1%	6·8%	28·3%		0·6%	8·1%

[10] Weber, *Trans Path. Soc. Lond.*, 1904, p. 288. [11] Bushnell, *Trans. Path. Soc. Lond.*, 1906, p. 455.

Some nucleated reds, normoblasts preponderating.

Post-mortem, forty-eight hours after death in hot weather. Liver, 59 ozs. Spleen, red and firm, 42 ozs. Marrow, red and increased in amount. Microscopically very cellular with absence of fat cells. Neutrophile myelocytes and mononuclears preponderating. Eosinophiles scanty. Many polymorphonuclears and lymphocytes. An excess of normoblasts. Liver capillaries choked with cells. Numerous small myelocytes and mononuclear cells with normoblasts, lymphocytes, and granular leucocytes. Spleen, moderate fibrosis. Pulp stuffed, myelocytes polymorphonuclear, and normoblasts.

Diagnosis: Leukanaemia (myelo-splenic anaemia).

Hurter[12]. Male, aged 17. For six months had suffered from weakness and breathlessness.

Admitted Aug. 8, 1904. Bleeding from gums. Liver and spleen not enlarged. No parasites or ova found in stools. Aug. 18, epistaxis; bleeding from uvula. Sept. 15, spleen felt. Sept. 17, bleeding from gums. The temperature rose before death, which occurred on Sept. 20, with cardiac failure. Whites, 6,000; Reds, 508,250; Hb. 15%; C. I., 1·5. 14,000 nucleated reds, nearly all megaloblasts.

		Sept. 15	Sept. 17
	%	%	%
Polymorphonuclears . . .	61·5	38	32
Lymphocytes	16·5	14·4	14
Large mononuclears	10·6	23	28
Neutrophile myelocytes . . .	10·6	23	27
Eosinophiles	0·8	0·8	0
Eosinophile myelocytes . . .	0	0·8	0

No mast cells seen on any occasion. Many erythroblasts, normoblasts preponderating towards end.

No post-mortem. Diagnosis: Leukanaemia.

A very cursory acquaintance with haematological literature reveals in addition to these many other cases coming within the four corners of Leube's definition which have been published under other names, such as 'Splenomegaly, with Anaemia and Myelaemia', Weil and Clerc[13]; 'Acute Myelocytic Leukaemia', Elder and Fowler, with references[14]; 'Atypical Leukaemia', Hirschfeld, with references[15]; 'Pernicious Anaemia ending in Leukaemia', Litten[16]. There are

[12] Hurter, *Liverpool Med. Chi. Journ.*, 1907, p. 108.
[13] Weil and Clerc, *Soc. de Biologie*, June, 1904.
[14] Elder and Fowler, *Edinburgh Med. Journ.*, Dec., 1904.
[15] Hirschfeld, *Fol. haematologica*, no. 3, 1904.
[16] Litten, *Berl. Klin. Wochenschr.*, 1877, nos. 19–20.

many others, and it is obvious even that pseudo-leukaemia infantum might be classified under this head.

This fact alone proves clearly enough that there is very great doubt whether the condition described by Leube can be considered as a distinct clinical or pathological entity, and the question arises whether the individual cases cannot be referred to one or other class of the already recognized blood conditions, and so rid us of the necessity for a term which, having no certain clinical or pathological meaning, leads only to confusion.

So far as the condition relates to the red cells as seen during life in Leube's case it is indistinguishable from pernicious anaemia. The extreme reduction to 256,000 per c.mm. of the red cells, the high colour index approaching 2; the very great variations in size, shape, and staining reactions of the individual corpuscles; the presence of megalocytes; the presence of many nucleated reds with a preponderance of megaloblasts make up a complete picture. Leube himself rejected this diagnosis on account of the large number of myelocytes (amounting to 1,380 per c.mm. and forming 13 per cent. of all the leucocytes) which were present in the blood, as well as the absence of siderosis in the liver and the scanty number of megaloblasts in the marrow. To these might be added the myeloid transformation found in the spleen. Leaving aside, however, all questions of the leucocytes and leucoblastic tissue, the present conception of pernicious anaemia is sufficiently broad, in the opinion of the writer, to allow of the anaemia in this case being considered as secondary.

It is known that the *blood picture* of pernicious anaemia may follow on post-haemorrhagic 'simple' anaemia as well as infections with bothriocephalus latus and other conditions. As Ehrlich has said, the same deleterious agents which are capable of producing a 'simple' anaemia may also cause the development of the progressive pernicious form. In the present connexion in Luce's case, this sequence of events was seen to take place. The patient, a woman of 40, was admitted to hospital on Feb. 4, 1902. On Feb. 13 the haemoglobin was found to be 65 per cent. From this point a gradual diminution took place, and on March 26 the reds were 2,428,000 and haemoglobin 35 per cent., the colour index being about ·6. No nucleated reds, whites 37,000. Shortly after haemorrhages appeared, and the number of red corpuscles steadily diminished, while the colour index rose. On May 16 the reds were 1,540,000, haemoglobin 35 per cent., colour index over 1; many microcytes, megalocytes, and normoblasts, a few megaloblasts. On June 16 megalocytes were present in large numbers. The anaemia remained of this type till death, the numbers of both varieties of nucleated reds, however, diminishing.

It is noticeable, too, in all the reported cases save Hirschfeld's, where the condition has been looked for, that siderosis has been absent from the organs after death, a fact suggesting a primary megaloblastic degeneration and not haemolysis as the cause of the anaemia.

When it is remembered that anaemia with megaloblasts in the blood is the

rule for all cases of even chronic myelocytic or 'mixed cell' leukaemia, and for some cases also of the lymphocytic form, as Leube himself admits, the higher degree of anaemia and the more marked development of the megaloblastic type where the condition, as in the cases under consideration, is severe from the onset and rapidly fatal, is not more than might be expected to occur.

It is probable that all cases of pernicious anaemia, even including Addison's anaemia, are secondary or symptomatic—the writer is certainly of that opinion—but some are obviously so. It seems justifiable, as well as preferable, therefore, in Leube's case to regard the anaemia as severe secondary anaemia, differing only in degree from the anaemia constantly seen in chronic myelocytic leukaemia. The same argument may be used for all the other cases quoted.

As has already been mentioned, the leucocyte side of these cases shows considerable differences. In Leube's case, as well as Weber's, Kerschensteiner's, and Bushnell's, for example, the number of whites was hardly, if at all, increased, and in the three latter at one time or other indeed was considerably diminished. In Hirschfeld's and the writer's cases, on the other hand, there appeared an increasingly large leucocyte count. In Körmöczi's, the leucocytes which had numbered 6,000 per c.mm. during the first fourteen days rose, during the last two days of life, to 107,000. The question of mere numbers has, in considering leukaemia and allied conditions, considerably less importance since it has been repeatedly shown that all the characteristic changes in the blood-forming organs may be present without any increase in the number of leucocytes in the peripheral blood, though a differential count will reveal the typical changes. Such cases form one class of the large group of so-called 'pseudo-leukaemias'.

In all the cases examined changes in the blood and blood-forming organs were found which would justify their classification under the head of leukaemia. As atypical or pseudo-leukaemia often enough, but still inseparable from the class as a whole as understood at present. When an attempt is made to classify them more exactly under the headings of lymphocytic or myelocytic, great difficulties are encountered.

A discussion of the origin of leucocytes, or the nature of leukaemia, is not the object of this paper, but it is impossible to discuss even the clinical diagnosis of these cases without a clear understanding of the terms in general use.

There is no more illuminating evidence of the change of opinion in regard to leukaemia than a consideration of the alteration in nomenclature during recent years. First, leucocythaemia or leukaemia, then the division into lymphatic and splenic forms, each with their proper blood picture. Next, the recognition of the importance of the bone-marrow with the adoption of the term spleno-medullary instead of splenic. After this, the substitution of medullary or myelogenic and the dropping of splenic as the importance of the spleen receded in estimation. Finally, the discovery of lymphatic cases with lesions limited to the bone-marrow, and the recognition that the type of cell found was of more importance than the mere situation of the pathological changes, leading to the terms lymphocytic or lymphoid on the one

hand, and myelocytic or 'mixed cell' on the other. Even now our difficulties are not at an end, and it is not impossible that we may complete the circle and return to a use of the term 'leukaemia', adding, as need be, a description of the changes found in the blood and blood-forming organs. Used in this way, of course the term leukaemia includes many conditions besides the classical forms of myelogenous and lymphatic. In the absence of any exact knowledge, however, as to the cause of any form of leukaemia, it is impossible to exclude from the class cases showing the characteristic changes in the blood and blood-forming organs.

When, owing to his own researches into the staining affinities of leucocytes for various aniline dyes a more accurate differentiation of these cells became possible, Ehrlich put forward a classification of them into two groups, unalterable and distinct at least during extra-uterine life. A. The cells bearing granules, whether neutrophile, eosinophile, or basophile. B. The non-granular cells, including the lymphocytes both large and small. The first group he regarded as arising exclusively in the marrow from similar mother cells (myelocytes), each according to its own type: the lymphocytes chiefly from the lymphatic glands, in part from other lymphatic structures, but definitely *not* from the bone-marrow.

In addition he described another type, the large mononuclear, non-granular, possessed of a rounded or oval nucleus, whose seat of origin he placed tentatively in the bone-marrow and possibly to some extent in the spleen. These cells he believed developed in the circulating blood into the 'transitional form' cells, with an indented nucleus bearing sparse granules, and might eventually reach the stage of polymorphonuclear cells.

It is agreed now that the marrow contains, as do most organs of the body, foci or islets of lymphadenoid tissue, and therefore, even in Ehrlich's sense, the bone-marrow may take part in the formation of lymphocytes.

It is universally held that, up to a certain point, in embryonic life all the cells of the blood, erythrocytes as well as leucocytes, are developed from an original 'indifferent' cell of the lymphoid type, with a single large oval nucleus and basophile non-granular protoplasm. From this cell, along different lines by a process of mitosis and differentiation, the granular leucocytes, the non-granular leucocytes, and the red cells arrive at their adult haemal forms.

Before birth the lymphadenoid and myeloid tissues having become completely differentiated the seats of origin of the granular and the lymphatic leucocytes become distinct. Ehrlich, Naegeli, and others believe that this distinction is never lost. Pappeheim, Hirschfeld, Grawitz, on the other hand, hold that under pathological and even normal states the foetal conditions persist to some extent or may be reverted to. This latter view is the one most widely held at present.

Leaving on one side the consideration of the normal state, there is abundant evidence that in leukaemic conditions of either type corresponding changes are found somewhere in the blood-forming organs. In lymphatic leukaemia the changes may be limited to a lymphoid transformation of the marrow or part of it;

in the myelocytic or 'mixed cell' form myeloid transformation of the spleen, liver or lymph glands may be found. That is to say, we may have a lymphatic leukaemia with changes limited to the bone-marrow and a myeloid leukaemia with changes in glands, liver or spleen. In frank cases of either type there is no difficulty in recognizing the anatomical changes, wherever found, as belonging naturally to that type and as certain to give rise to the changes which have been found reflected in the blood during life. It is in the consideration of atypical cases that difficulties arise. The cell round which most of the discussion rages is the large mononuclear leucocyte. It is certain, though not every one will admit it, that to distinguish between the original indifferent cell, or some of its more nearly related descendants, and large lymphocytes is a matter often of extreme difficulty or impossible.

In lymphocytic leukaemia in the acute form, but sometimes also in the chronic, large mononuclear cells appear in large numbers in the blood. In certain 'aleukaemic' leukaemias or pseudo-leukaemias, too, they may be present in *relatively* large numbers, where the total leucocyte count is not increased. In such cases, as has been already said, the change found in the blood-forming organs is a lymphoid transformation, and this may be limited to the marrow. In the absence of any myeloid transformation in the tissues, or of any marked changes at any time in the number or proportion of the granular cells in the blood, there can be no hesitation in classing such cases as lymphocytic leukaemia. The precise name given to the cell, whether large lymphocyte, large mononuclear, or even original least differentiated cell, seems to the writer immaterial, for even if the type has reverted back to its earliest original form it remains lymphocytic in nature if it has arisen from adult lymphadenoid tissue, or any other cell in the direct line of descent (cf. carcinoma and sarcoma). The presence of a few neutrophile myelocytes in the blood at the same time does not invalidate this argument, for they have a readily understood origin in the still remaining myeloid tissue, and bear a significance comparable to those myelocytes seen in transitory conditions such as specific fevers.

In myelocytic leukaemia, now often called 'mixed cell', the blood picture is an extraordinarily varied one. In addition to the cells universally recognized as being of myeloid descent, those which are quite as certainly of lymphatic origin, for instance small lymphocytes, are present in very large numbers, though this fact is obscured in their relative diminution.

When under these circumstances large mononuclear cells appear in the blood it is impossible often enough to decide whether they belong to the myeloid or lymphadenoid branch of the leucocyte tree. Clinically the point is of no importance, and we may rest content with acknowledging our ignorance. It is certain, nevertheless, that they are often myeloid in nature, pro-myelocytes as they have been called.

In examining the published cases of 'leukanaemia' this obviously is so. In Leube's case 29 per cent. of the neutrophile myelocytes were completely non-granular, and at the same time 25 per cent. of the polymorphonuclears were also

free from granules. In the writer's case, too, a similar condition, if less marked, was present. Very striking evidence in this direction is given in a case published by Melland [17], in which, under observation, the blood picture changed from a myelocytic to a lymphocytic, the final count showing only 7·2 per cent. of polymorphonuclears and 4 per cent. of neutrophile myelocytes. The change was gradual, but no one can doubt that the blood remained myelocytic to the end.

Accepting then the view that large mononuclear cells may be lymphocytic or myelocytic, it must be admitted that a true myelocytic leukaemia may simulate all the appearances of the lymphocytic form as in Melland's case. Further, that some cases heretofore described as lymphatic leukaemia may be of this nature, that is to say, not merely characterized by their situation in the marrow, but arising primarily from cells which have belonged to the myelocytic or granular leucocyte branch of the leucocyte tree.

As regards the cases of leukanaemia collected in this paper, Zevi and Teeter's cases are mere transient blood conditions, and cannot rightly be included under the head of leukaemia at all. In Hurter's case no post-mortem examination was made. Leube, Hirschfeld, and the writer's cases both on the blood picture and post-mortem appearances, as well as Körmöczi's chiefly on the latter ground, he would class as atypical myelocytic or 'mixed cell' leukaemias. In the same way Weber's, Bushnell's, and Kerschensteiner's cases would fall into the sub-group of atypical myelocytic leukaemia with aleukaemic or 'pseudo-leukaemic' blood condition. Luce's case seems to belong to the lymphocytic type, and in Mattirolo's case the details given are not sufficiently precise to warrant an opinion being given, but even in these cases the writer is by no means certain that they do not belong to the mixed cell type.

Conclusions.—That within the term of Leube's definition there may and have been described different conditions having only a superficial resemblance. The term is therefore misleading, useless, and its use might be abandoned.

That the majority of cases so far described under this head belong to the group of atypical myelocytic leukaemias, and might properly be described under that name.

That acute myelocytic or 'mixed cell' leukaemia is a much commoner condition than is generally supposed.

[17] Melland, *Trans. Path. Soc. Lond.*, 1906, p. 111.

A CLINICAL SPHYGMOMANOMETER YIELDING ABSOLUTE RECORDS OF THE ARTERIAL PRESSURE

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With Plates 14–19

The want of some graphic record of the absolute height of the manometric tracing has been a serious deficiency in our sphygmomanometers. Even the ingenious and excellent instrument of Erlanger does not in itself provide evidence of the arterial pressure, and the height of the column of mercury requires to be read by the observer when taking tracings and written on the record afterwards. It must be obvious that distinct advantages are to be gained from the automatic registration of the level of the mercurial column; and the attempt to furnish a means for obtaining such a record has occupied much of my attention for some time. The difficulties in obtaining a direct tracing from the mercurial manometer seem to weigh very heavily upon those who have experimented with the sphygmomanometer, as may be seen from the work of Janeway,[1] who holds that a liquid so heavy as mercury cannot possibly follow rapid variations in cardiac and respiratory pressure. In my opinion those difficulties have been considerably exaggerated, and the same arguments apply with equal force to the use of the kymograph in physiological investigation. With the skilful assistance of Mr. Ednie of the Physiological Department of the University the difficulties have been overcome, and excellent results have been obtained, with the apparatus designed by me.

The instrument consists of a circular armlet containing a rubber bag, as in the instrument of Riva-Rocci, which is brought by means of a rubber tube into direct communication with a mercurial manometer. The tube is in connexion with a large syringe, similar to a nasal inflator, which is used for raising the pressure in the bag of the armlet, and is provided with a valve by means of which the pressure may be lowered either rapidly or slowly. The lumen of the U-tube containing the mercury is the same as that of the ordinary physiological kymograph. Upon the mercury rests the float, surrounded by alcohol, which permits of free movement, and the upright rod, made of aluminium, terminates in an arm of the same metal, which writes on the revolving cylinder. Another arm traces upon the cylinder the abscissa

[1] *The Clinical Study of Blood Pressure*, 1904, p. 5.

[Q. J. M., Oct. 1907.]

marking the absolute zero of the column of mercury. The cylinder is driven by clockwork placed horizontally, as in the Erlanger instrument. In order to record the exact instant when the blood returns to the artery below the point of compression, which, as is now usually accepted, is taken as the criterion of the systolic pressure, its movements are also recorded on the cylinder. This is done by means of a tambour brought into contact with the brachial or radial artery, as the case may be, through a pelotte which rests upon the vessel. It is adjusted to the arm by means of two horizontal bars clamped together by two vertical screws. The tambour is in communication with another tambour recording its movements in the ordinary way by means of a lever which writes upon the cylinder. We have found that the best tracing is obtained by employing a larger tambour in contact with the artery than that connected with the recording lever—in fact the former is twice the size of the latter. The instrument is shown in Fig. 1.

When using the instrument the cuff is adjusted to the arm, and the tambour to the artery below. The pressure is then raised with one steady, forcible expulsion of the air contained in the syringe, until a high level is reached—in ordinary circumstances 150 or 160 mm. Hg. being sufficient. The valve, being already set at the slow escape, allows the pressure at once to fall gradually. If sufficient pressure has been employed, the tracing from the artery shows complete absence of all movements, and the curve resulting from the gradual lowering of the column of mercury is almost destitute of all oscillations. After a short time, however, the manometric tracing shows some minor fluctuations which gradually increase. The instant that the arterial pressure overcomes the resistance, small waves begin to appear in the arterial tracing. Occasionally, as was noticed by von Recklinghausen,[1] Janeway,[2] and Masing,[3] in observations made by taking tracings, either with the sphygmograph or plethysmograph, from the fore-arm, one or two little waves show themselves, but in most cases the return of the pulsation is marked by the appearance of definite waves. The mode of application of the instrument is shown in Fig. 2.

Some of the tracings obtained by this instrument are shown in the following pages, and need but little explanation. In all of them the tracing obtained by the tambour from the artery is at the foot; the abscissa is immediately above this, and the manometric tracing starts from this level.

Since the manometer has a double column of mercury in the U-tube, the height of the tracing above the abscissa must be doubled in reading the record; i.e. if the tracing at any point should be 65 mm. from the abscissa, the pressure at that point must be put down as 130 mm. Hg.

There is not the least difficulty in determining the maximum, or systolic, pressure, since it is the level at which the pressure within the artery overcomes

[1] *Archiv für experimentelle Pathologie und Pharmakologie*, 1901, Band xlvi, S. 78.
[2] *New York University Bulletin of the Medical Sciences*, 1901, vol. i, p. 105.
[3] *Deutsches Archiv für klinische Medicin*, 1902, Band lxxiv, S. 253.

the resistance of the band, and can be ascertained by the earliest movement of the lever in connexion with the vessel below the band, as has already been described. The determination of the minimum, or diastolic, pressure, is a matter of much greater difficulty. It is certain that the point at which the greatest amplitude of pulsation is recorded corresponds with a state of matters in which the pressure within the vessel and that within the surrounding band are most nearly equal, thus allowing free play to the oscillations of pressure within the artery; it is probable that this level furnishes an approximation to the minimum, or to a point somewhere between the minimum and the mean pressure. For practical purposes it is well to assume that the lowest point of the largest wave is an index to the minimum pressure.

The first tracing (Fig. 3) was obtained from a healthy man of middle age, and it is of interest as showing that, although the systolic pressure at this period of life, under conditions which may be termed normal, is little above the average of the youthful adult, the diastolic is decidedly high.

An instance of mitral obstruction and cardiac failure furnished the opportunity of obtaining Fig. 4, which was taken after the patient had improved very much as the result of prolonged rest and tonic treatment. It shows, nevertheless, in addition to a somewhat low systolic, and rather high diastolic, pressure, a great amount of irregularity and inequality.

A striking contrast is afforded by Fig. 5, obtained from a case of aortic obstruction and regurgitation. In this example, along with a normal maximum, there is a very low minimum pressure, and there is almost perfect rhythm of pulsation and equality of impulse, only slightly modified by indications of Traube-Hering waves.

The patient from whom Fig. 6 was obtained was also an instance of aortic disease, both obstructive and regurgitant, but with much less difference between maximum and minimum pressure. The same steadiness of rhythm and equality of wave, however, is seen in this tracing.

The case of early arterial sclerosis from which Fig. 7 was taken shows that, in spite of the thickening of the arteries, the systolic pressure was not increased above the normal, while the diastolic pressure was not above the average.

Advanced arterial degeneration, followed by an attack of cerebral haemorrhage, afforded the opportunity of obtaining Fig. 8. In this tracing a maximum pressure of 200 or more was constantly observed, with a minimum of about 160, except when the patient was under the influence of the nitrites. The tracing is of interest as showing variations in the curve, probably of the nature of Traube-Hering oscillations of pressure, but occurring with remarkable infrequency.

Another patient suffering from arterial sclerosis yielded the tracing shown in Fig. 9. He was an elderly man who presented marked features of interstitial nephritis, and who had, during the present year, been in my ward with threatened cerebral symptoms, and a pressure of over 300. When the tracing was taken the pressure had fallen considerably, but with the diminution there were

indications of cardiac failure, shown in the tracing by irregularity and inequality of pulsation.

Early tabes dorsalis in a man who had reached early middle life gave the occasion of securing Fig. 10, which is of much interest, as proving that this disease may be associated with low pressure. The sudden rise in the manometric record, followed by a fall in the arterial tracing, was the result of a cough.

The last tracing, Fig. 11, shows the pressure in a patient suffering from dementia paralytica. The maximum was absolutely normal for his age, about thirty years, but the minimum was rather above the average. The tracing shows most beautifully the occurrence of frequent and almost rhythmic Traube-Hering curves.

It is a pleasant duty to acknowledge my indebtedness to Mr. Ednie, of the University Physiological Laboratory, for the skill with which he has carried out my ideas in the construction of the instrument, and to express my obligations to my House Physicians, Dr. G. A. Gordon and Dr. A. I. Shepheard-Walwyn, for their devotion in making the observations which have been recorded in this paper.

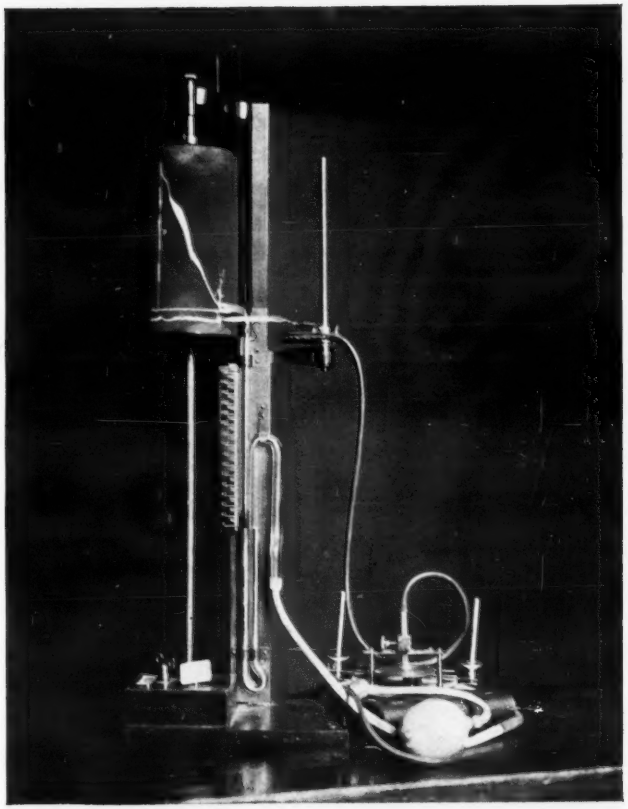

FIG. 1. The Sphygmomanometer unattached to the arm.

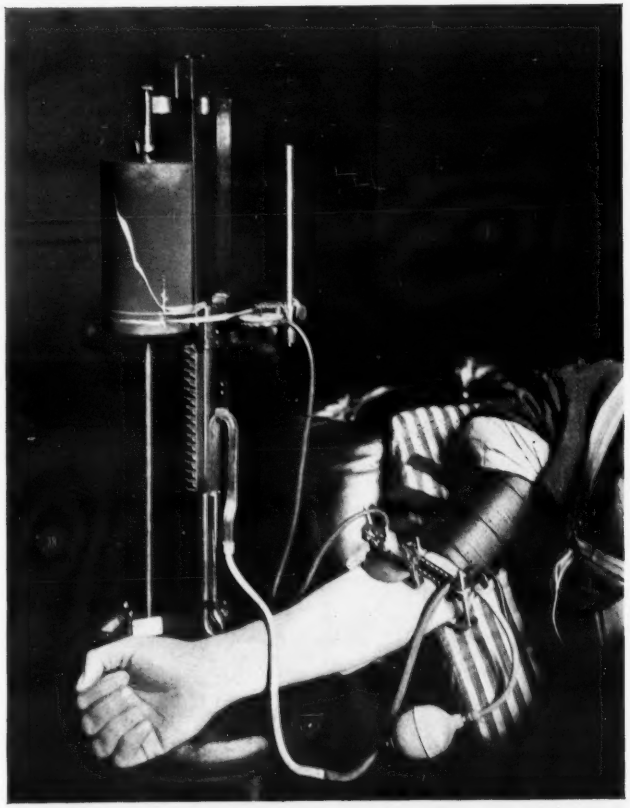

FIG. 2. The instrument applied to the right arm.

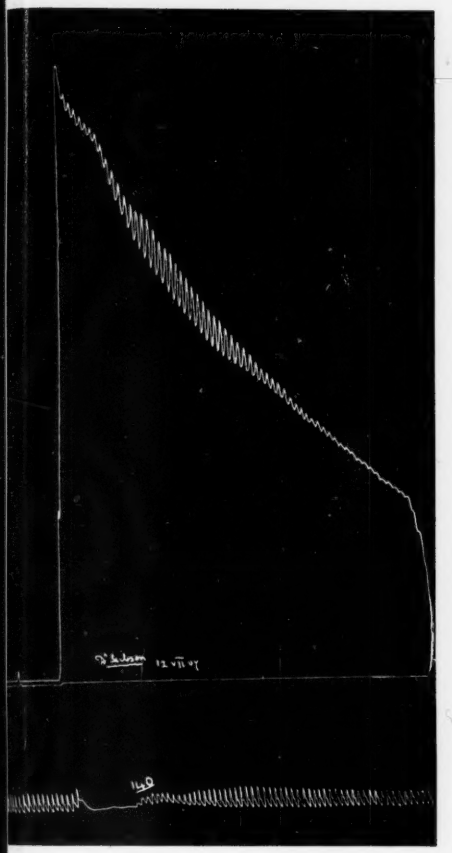

FIG. 3. Tracing from the right arm of a healthy man. Maximum 140; minimum 122.

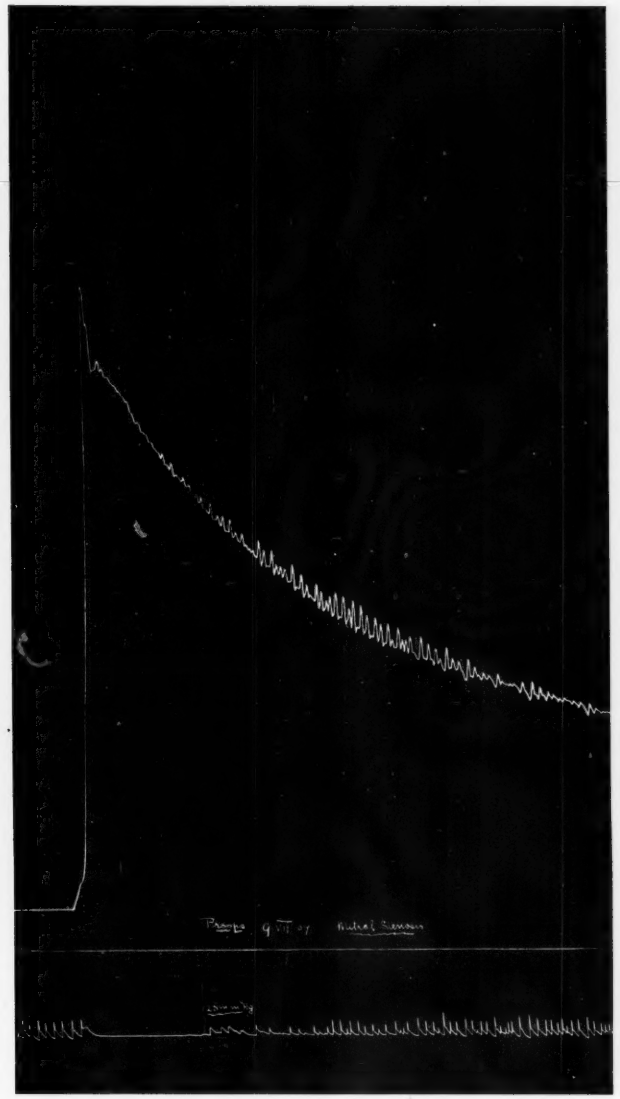

FIG. 4. Tracing from a case of mitral obstruction and cardiac failure, showing irregularity and inequality. Maximum 125; minimum 96.

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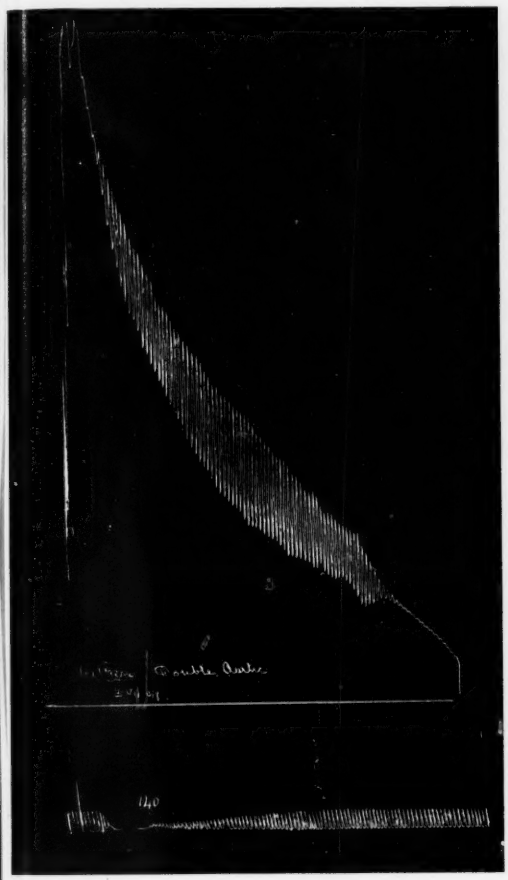

FIG. 5. Tracing from a case of aortic obstruction and incompetence. Maximum 140; minimum 58.

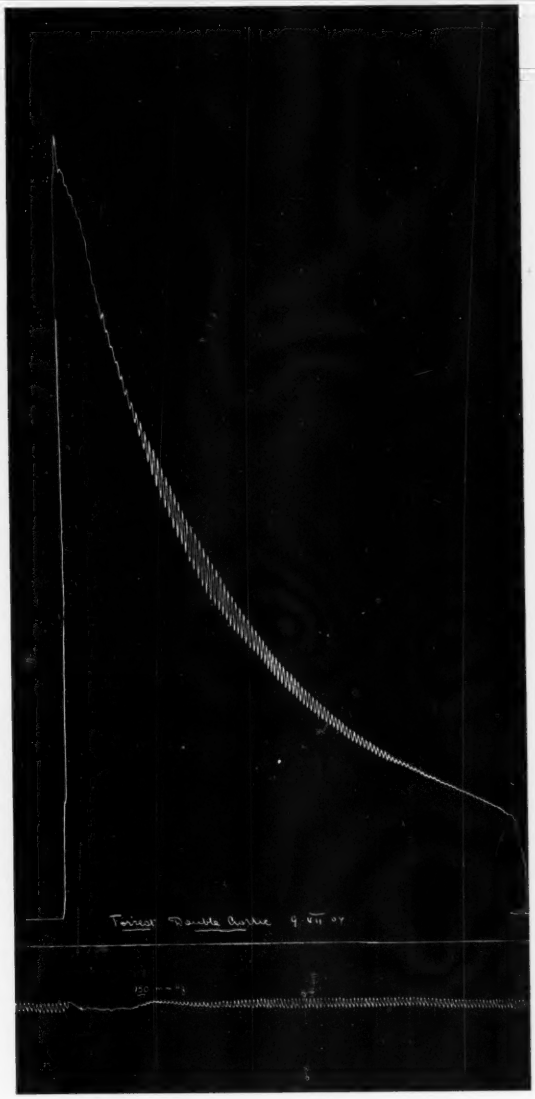

FIG. 6. Tracing from a case of aortic obstruction and incompetence. Maximum 150; minimum 105.

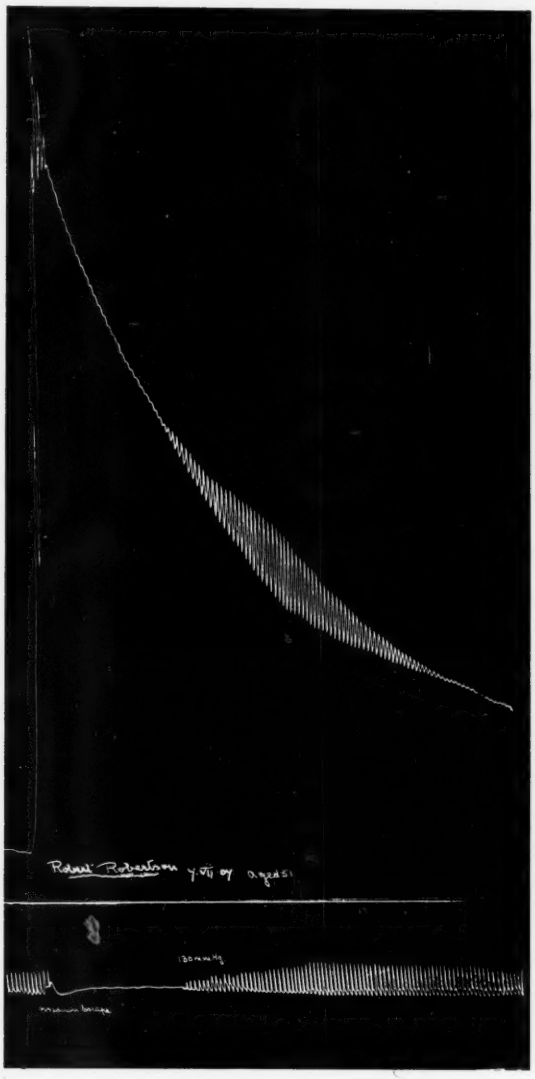

FIG. 7. Tracing from a case of early arterial sclerosis. Maximum 130; minimum 90.

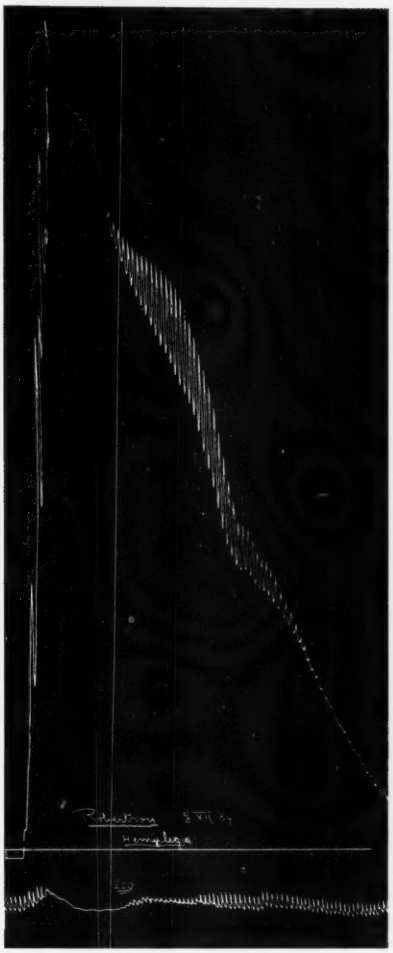

FIG. 8. Tracing from a case of arterial sclerosis and hemiplegia from cerebral haemorrhage. Maximum 200; minimum 160.

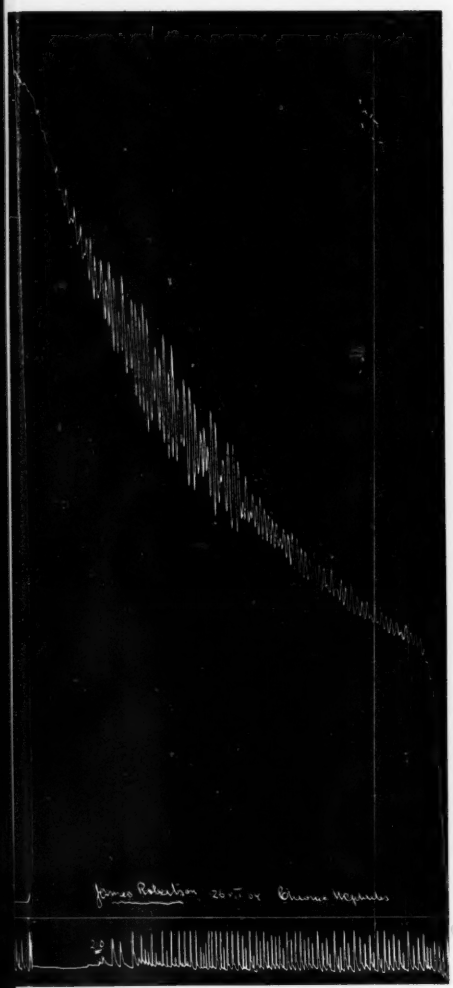

FIG. 9. Tracing from a case of arterial sclerosis and interstitial nephritis, with commencing cardiac failure, irregularity and inequality. Maximum 210; minimum 148.

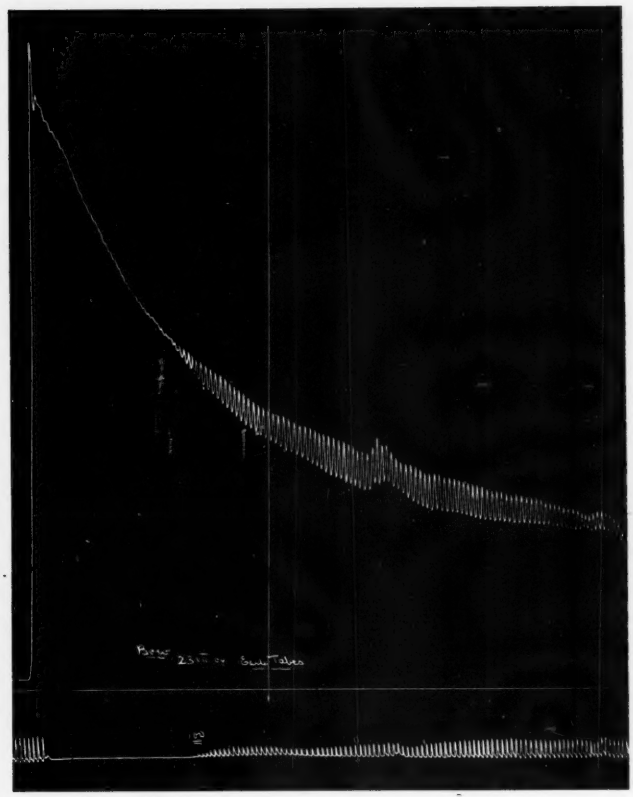

FIG. 10. Tracing from a case of early Tabes dorsalis. Maximum 100; minimum 60.

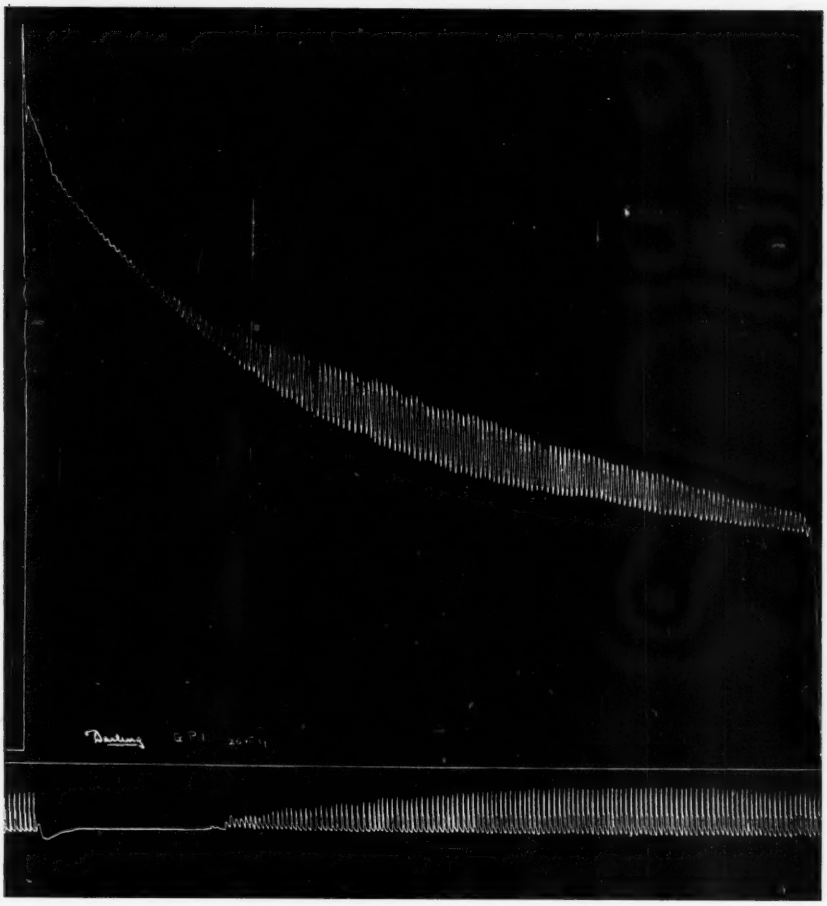

FIG. 11. Tracing from a case of early but swiftly advancing general Paralysis. Maximum 130; minimum 94.

THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THE FIRST ANNUAL MEETING took place on May 23 and 24 in London, at the rooms of the Royal Medical and Chirurgical Society. Two morning meetings and two afternoon meetings were held. Demonstrations of patients and of instruments were given from 2 to 3 p.m. each day, and a dinner was held on the evening of May 23. One hundred and fifty-five members attended the meeting.

MAY 23. *Morning Meeting.* After the rules had been passed and the officers elected, several communications were made upon diseases of the blood: on polycythaemia (by H. H. Tooth), on anaemia with enlarged spleen in young adults (by J. M. Cowan), on splenic anaemia (by Morley Fletcher), on leukanaemia (by C. H. Melland), on acute myelogenic leukaemia (by J. H. Drysdale), and on acute abdominal symptoms with lymphocytosis (by R. J. M. Buchanan). These communications gave rise to an interesting discussion. Most of the speakers confined themselves to the histological diagnosis, in which it was allowed on all sides that much remained still unsettled. It was also urged that attention should not be concentrated upon this side alone, but that more effort should be made for an etiological classification.

Demonstrations. A scheme representing the pressure in the vascular system—and many microphotographs of normal and diseased arteries (by W. Russell). Progressive changes in the blood from a case of leukanaemia (by C. H. Melland). Many rare and interesting clinical cases were shown.

Afternoon Meeting. James Mackenzie related the histories of several cases observed through many years, in which, as the patient became worse, the evidence of auricular systole (viz. a presystolic murmur and an auricular wave in the venous sphygmogram) disappeared, and the ventricular systole could alone be recognized. He ascribed this to disease of the sino-auricular node. A. Keith (introduced), who had examined the hearts of these patients after death, felt obliged to say that there was yet no histological evidence for this hypothesis. In the very lively discussion which followed, some speakers upheld Mackenzie's views, others argued that the dilatation of the auricle might so diminish its contractility as to abolish the evidence of contraction, and others referred the change to a greater power of suction put forth by the ventricle.

Other communications were—A case of microbic cyanosis due to *B. Coli* (by G. A. Gibson), cases of rheumatic aortitis (by Prof. Clifford Allbutt), cases with severe cardiac symptoms due to reflex disturbance from the bladder (by Prof. Little), tricuspid without mitral stenosis (by Wardrop Griffith), on sulphur as an intestinal antiseptic (by Prof. Wild), and on acute myxoedema (by the late Prof. Dreschfeld).

The Dinner was attended by 134 members and guests. Sir Richard Douglas Powell was in the chair. A meeting of the Executive Committee was held after the dinner, at which Dr. Gibson's invitation to Edinburgh for the Annual Meeting of 1908 was accepted, and business concerning the *Quarterly Journal of Medicine* was discussed. It was agreed that the proposal of the Clarendon Press was satisfactory.

An Editorial Committee was appointed, who should be assisted by a body of collaborators to be invited by the Editorial Committee, and it was decided to subscribe for the *Journal* at the rate of one guinea for each member of the Association.

May 24. *Morning Meeting.* Communications were received—On the occurrence of leucin and tyrosin in the urine in cases of cardiac liver (by Prof. Dixon Mann), showing that this phenomenon is not confined to organic disease of the liver, nor to fatal cases. On some prolonged cases of haematoporphyrinuria (by T. K. Monro); it was agreed that the colour in these cases was not due to haematoporphyrin, but to some other pigment which remained when all the former body had been removed, also that some of these cases are lifelong. On the treatment of diabetes by secretin (by A. P. Beddard); many present had tried it, and no one had found it of use. On cryoscopic examination of the urine and blood (by Bell Walker, introduced); the author stated that if the specific gravity were taken after removal of albumin cryoscopy gave no additional information when applied to the urine, but was of some use when carried out on the blood. On an epidemic of diphtheria without a faucial membrane (by Sir John Moore); a brisk discussion arose on the difficulty of disinfection, and on bacteriological diagnosis. On cases of multiple hereditary telangiectases with recurring haemorrhages (by Prof. Osler). On three unusual cases (by Hale White), which were (1) cystin calculus, (2) myxoedema caused by removal of an aberrant thyroid from the back of the tongue, (3) pernicious anaemia with pigment in the buccal mucous membrane. It was agreed that pigment had not been produced in this situation by arsenic.

Demonstrations. Some very unusual clinical cases were on view, and Dr. Dennis Embleton (introduced) exhibited some inventions to facilitate the counting of microscopic objects. They were adaptations of the electric markers used in billiard rooms.

Afternoon Meeting. Dr. Head gave a demonstration of the tracks of sensory impulses.

Communications were received—On the nervous symptoms produced by the presence of cervical ribs (by H. Lewis Jones, and C. M. Hinds Howell, introduced); on intermittent limp (by E. S. Reynolds); on certain constituents of the urine in diseases affecting the muscles (by E. I. Spriggs); on cases of optic neuritis (by R. A. Fleming); on suprarenal sarcoma in children with metastasis in the skull (by R. Hutchison); and on the advantage of giving very large doses of salicylate of sodium in cases of rheumatism and chorea (by D. B. Lees).

It was found impossible to get through all the material at the disposal of the meeting.

THE PATHOLOGY OF THE CEREBRO-SPINAL FLUID DERIVED FROM LUMBAR PUNCTURE

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With Plate 20

This communication is based on the results of examinations of the cerebro-spinal fluid obtained by the operation of lumbar puncture on 140 cases at the Hospital for Sick Children during the last three years. The examinations recorded include: 57 cases of tuberculous, and 36 of meningococcal meningitis, 16 cases in which other organisms were found in the fluid, e. g. pneumococcus, streptococcus, staphylococcus and B. coli communis, 3 cases of syphilitic meningitis, 14 cases in which cerebral conditions other than meningitis were present, e. g. abscess, tumour, sclerosis and hydrocephalus, and 14 cases with meningeal symptoms due to whooping cough, broncho-pneumonia and acute gastro-enteritis.

I. *Tubercle bacillus* the causative organism. In 47 cases the cerebro-spinal fluid obtained by lumbar puncture was verified as tuberculous by post-mortem results in 19, or by the finding of tubercle bacilli in the fluid during life in 27 cases, in one case tubercle bacilli were found only in a discharge from the ear. During the last ten months (Dec. 1906–Sept. 1907) tubercle bacilli have been found in 25 out of 31 specimens (= 80 %).

This success has been due to adopting the simple method of staining the fine lymph clot, which usually forms on standing, in which the bacilli can be easily recognized without prolonged search.

Examination of cell deposit obtained by centrifugalizing fluid.

1. Lymphocytes in excess in 31 cases.

Marked lymphocytosis is recorded in 24 cases without differential count. Differential counts of 200 or 300 cells recorded in the following 7 cases.

(*a*) In 1 case Lymphocytes = 97·5 %. Polymorphonuclears = 2·5 %.

(*b*) In 3 cases Lymphocytes = 91 %. Polymorphonuclears = 9 %.

(*c*) Lymphocytes = 84 %. Polymorphonuclears = 15·5 %. Eosinophiles = ·5 %.

Post-mortem. Marked tuberculous meningitis with tuberculous nodules in the cerebellum, and chronic pulmonary tuberculosis.

(*d*) Lymphocytes = 52·5 %. Polymorphonuclears = 47·5 %.

Post-mortem. Much tuberculous lymph at the base of the brain and spinal meningitis.

(*e*) Lymphocytes = 50 %. Polymorphonuclears = 50 %.

In 22 of these 31 cases tubercle bacilli were found in the lymph clot.

2. Polymorphonuclears in excess in two cases.

(*a*) Blood-stained fluid—many leucocytes chiefly polymorphonuclears. Blood clot treated by Jousset's digestion method—one tubercle bacillus found.

Post-mortem. General tuberculosis—chronic tuberculous meningitis with subdural tuberculous nodules.

(*b*) Much cell deposit.

Cell count. Polymorphonuclears = 71·3 %. Lymphocytes = 28·6 %.

Many tubercle bacilli found in the lymph clot.

Culture. Sterile.

Post-mortem. Not obtained.

3. A few lymphocytes or degenerated cells found in 11 cases, verified by post-mortem examination, and by the finding of tubercle bacilli in one case.

4. No cells found in two cases.

Post-mortem. Tuberculous meningitis in both with hydrocephalus in one, the medulla being closely adherent to the cerebellum.

5. In one case the cells present were chiefly lymphocytes—but no tubercle bacilli were found.

Post-mortem. No meningitis. General tuberculosis with tuberculous masses in the cerebrum and attached to the dura mater.

The examination of the cell deposit obtained by centrifugalizing the fluid showed that in the majority of cases lymphocytes formed the bulk of the cell deposit more particularly in the later stages. They might be the only cells present and where cell counts were recorded the percentage varied from 28·6–97·5 %.

Polymorphonuclears were found in amounts varying from 2·5–71·3 %.

In the few cases in which they occurred in excess, it would appear from clinical and post-mortem evidence that their predominance was associated with a chronic condition terminating acutely, indicated by a large amount of plastic lymph and many tuberculous nodules.

The presence of albumin was recorded in 30 cases; there was a marked trace in 12, slight trace only in 18.

In the majority of specimens the fluid was quite clear, in others it yielded a visible cell deposit and became opalescent on shaking.

In one specimen the deposit was composed of a few lymphocytes and many minute colourless rhomboid crystals, obtained after evaporation on the slide, the occurrence of which is described at the end of this paper.

Cultures made from the fluid of the total of 47 cases proved sterile in 39, but contaminations were present in 8.

Ten additional cases were diagnosed as tuberculous meningitis, but could not be verified.

Lymphocytes were the only cells found in the cerebro-spinal fluid in excess in three cases, scanty in five, and no cells could be seen in two specimens. Albumin was present in slight traces.

II. *Meningococcus* the causative organism. Examinations of the cerebro-spinal fluid obtained by lumbar puncture were made in 36 cases.

1. Sixteen cases (= 44 %), two of which were cerebro-spinal meningitis, with petechial haemorrhages, and 14 simple post-basic meningitis.

Films from the cell deposit showed a marked excess of polymorphonuclears varying from 65–94 %, also intra- and extra-cellular Gram negative diplococci resembling meningococci.

Cultures yielded pure growths of the meningococcus on agar, serum or nutrose agar in each of the 16 cases. In addition the meningococcus was obtained from the heart's blood at the post-mortem examination of the two cases of cerebro-spinal meningitis.

2. Eleven cases (= 30·5 %) of simple post-basic meningitis.

Film preparations showed a cell deposit chiefly composed of polymorphonuclears with a few Gram negative diplococci resembling meningococci.

Cultures. Sterile.

3. Three cases (= 8·5 %).

Film preparations showed a scanty cell deposit chiefly composed of polymorphonuclears, but no meningococci.

Cultures. Sterile.

One case 'recovered', one was verified post-mortem, and in one the result was not ascertained.

4. Six cases = 17 %.

Film preparations showed a scanty cell deposit chiefly or entirely composed of lymphocytes or degenerated cells with a few degenerated diplococci.

Cultures. Sterile.

Two cases were verified post-mortem, meningococci being found in films and obtained in pure cultures from the ventricular fluid.

Two cases recovered.

In two, hydrocephalus resulted and the patients were discharged *in statu quo.*

One case should be mentioned in which the diagnosis would have been assisted by lumbar puncture; the illness was of acute onset and lasted 48 hours, with high fever and petechial eruption. At the post-mortem examination well-marked cerebro-spinal meningitis was found.

Film preparations from the ventricular fluid showed an excess of polymorphonuclears and intra-cellular meningococci. The meningococcus was also obtained in culture from the ventricular fluid and the heart's blood.

Of the 36 cases examined by lumbar puncture, 11 were verified post-mortem, 12 made partial or complete recovery, and two were discharged with hydrocephalus. In the remaining 11 cases the subsequent course could not be ascertained.

A survey of the results of the examination of cerebro-spinal fluid shows that in severe fatal cases of meningococcal meningitis, and in the acute stages of those which eventually recover, the fluid is often turbid, contains a heavy trace of albumin, and a large number of polymorphonuclear cells, with meningococci identified in film preparations and culture.

In the less acute cases the fluid is frequently clear and contains a faint trace of albumin; the cell deposit is scanty but still chiefly composed of polymorphonuclears, with a few meningococci in film preparations, but not usually obtained in culture. In the chronic cases, which may eventually recover or result in hydrocephalus, the fluid is clear—no albumin or the merest haze is present—and the only cells found are a few lymphocytes often degenerated; film preparations show no organisms or only a very few degenerated diplococci. Cultures are sterile.

III. *Pneumococcus*—found in nine cases.

1. In four cases the cell deposit was chiefly composed of polymorphonuclears.

(*a*) Albumin, faint haze—cells scanty, but chiefly polymorphonuclears. Pneumococci in film preparations and pure culture.

Post-mortem. Pneumococcal meningitis, peritonitis and empyema.

(*b*) Albumin, heavy deposit—many cells. Polymorphonuclears = 70%; Lymphocytes = 30%. Pneumococci obtained in film preparations and cultures.

Post-mortem. Not obtained.

(*c*) Albumin, marked trace—cells scanty, chiefly degenerated polymorphonuclears. Small colourless rhomboid and fusiform crystals. Films showed abundant pneumococci.

Post-mortem. Pneumococcal meningitis.

Film preparations showed many polymorphonuclears but no organisms.

Culture. Mixed growth of bacilli and cocci.

Post-mortem. Pneumococcal meningitis.

2. In two cases the only cells present were a few lymphocytes.

(*a*) Pneumococcus in pure culture.

Post-mortem. Not obtained.

(*b*) Case of pneumonia with meningeal symptoms in the early stage, resulting in recovery.

Diplococci resembling pneumococci found in film preparations.

Culture. Sterile. No albumin.

3. In two cases the cerebro-spinal fluid during life was clear and showed no cells or organisms in film preparations.

Cultures. Sterile.

Post-mortem. Well-marked pneumococcal meningitis was found.

4. One case, in which tuberculous meningitis was found at the post-mortem, pneumococci were obtained in film preparations and pure culture from the cerebro-spinal fluid during life, probably as a secondary infection.

IV. *Streptococcus* in five cases.

1. Few leucocytes. Streptococcus in film preparations and pure culture.

Post-mortem. Streptococcal meningitis secondary to otitis media.

2. Case of acute anterior poliomyelitis, during life no organisms or cells were recognized in the fluid and the culture was sterile.

Post-mortem. Film preparations from the spinal meninges showed streptococci. Culture from the cerebro-spinal fluid yielded streptococcus in pure growth.

3. Streptococcus obtained from the cerebro-spinal fluid during life.

Post-mortem. Streptococcal meningitis.

4. Fluid from two cases of Spina bifida showed the presence of an excess of polymorphonuclears and streptococci in film preparations and pure culture. Streptococci were also obtained in culture from the fluid at the post-mortem examination.

V. *B. coli communis* in one case.

Fluid from a case of Spina bifida showed a heavy trace of albumin, abundant polymorphonuclears and bacilli in film preparations, and pure growth of B. coli communis in culture. Recovery followed.

VI. *Staphylococcus pyogenes aureus* obtained in films from deposit, and in pure culture. Cells chiefly polymorphonuclears.

Post-mortem. Purulent meningitis of brain and cord.

VII. *Chronic meningitis* secondary to congenital syphilis (?), three cases.

1. Scanty lymphocytes only.

Culture. Sterile.

2. First examination, albumin, well-marked trace.

Cell count. Lymphocytes = 92 %. Polymorphonuclears = 8 %.

Culture. Sterile.

Second examination, albumin, faint trace.

Cell count. Lymphocytes = 95·5 %. Polymorphonuclears = 4·5 %.

Culture. Sterile.

3. Albumin, marked trace—heavy cell deposit of lymphocytes and endothelial cells. No organisms found.

Post-mortem. Chronic plastic meningitis, cortical sclerosis and hydrocephalus.

VIII. Cerebral conditions other than meningitis.

1. *Cerebral abscess*, two cases.

(*a*) Few degenerated cells only. No organisms found.

Post-mortem. Pus from right lateral ventricle yielded staphylococcus pyogenes aureus in pure culture.

(*b*) Albumin, faint haze—very few leucocytes. No organisms found.

Culture. Sterile.

Leucocyte count of blood = 18,500 per c.mm. Pus from temporo-sphenoidal abscess yielded streptococcus in pure culture.

2. *Polio-encephalitis.* Cell deposit composed of scanty lymphocytes and numerous crystals. No organisms found.

3. *Cerebellar tumour.* Probably tuberculous. Three cases. No albumin. Very few lymphocytes only. No organisms found. *Culture.* Sterile.

4. *Cerebral sarcoma.* One case. No albumin. No cells or organisms found in cerebro-spinal fluid.

5. *Cerebral sclerosis.* Two cases.

(*a*) Albumin, faint haze.

Film preparations from centrifugalized fluid showed red blood corpuscles and scanty lymphocytes. *Culture.* Sterile.

Post-mortem two weeks later—marked cerebral sclerosis—no evidence of meningitis.

(*b*) No cells or organisms found. *Culture.* Sterile.

6. *Hydrocephalus.* Five cases, not secondary to post-basic meningitis.

(*a*) Albumin, trace. Few lymphocytes. *Culture.* Sterile.

Patient discharged *in statu quo.*

(*b*) Scanty leucocytes. Many crystals (v. infra). The patient died of purulent meningitis secondary to operation of trephining.

(*c*) Albumin, slight trace.

Cell count. Polymorphonuclears = 64 %. Lymphocytes = 36 %. At post-mortem examination simple hydrocephalus only found.

(*d*) Alkaline, sp. gr. 1010. Albumin deposit = $\frac{1}{2}$. Cells present. Scanty red blood corpuscles and leucocytes. Chlorides and phosphates in excess, sulphates, trace. At post-mortem examination simple hydrocephalus only found.

(*e*) Hydrocephalus with cerebral sclerosis. Cells present, chiefly lymphocytes. No organisms found.

IX. Fourteen cases presenting meningeal symptoms were negatived by examination of cerebro-spinal fluid and by subsequent course.

1. *Whooping cough with convulsions.* Six cases.

Post-mortem. No evidence of meningitis. No organisms or cells found. Albumin absent or present in faint traces in three cases, heavy trace in one. In one case a few degenerated cells and crystals (v. infra) were found.

2. *Broncho-pneumonia.* Five cases.

(*a*) With fatal convulsions. Albumin trace. Few degenerated lymphocytes. *Culture.* Sterile.

Post-mortem. No evidence of meningitis.

(*b*) With otitis media. Recovery. Scanty degenerated cells. *Culture.* Sterile.

(*c*) With empyema. Scanty cells, chiefly lymphocytes in cerebro-spinal fluid. *Culture.* Sterile.

Post-mortem. No evidence of meningitis.

(*d*) Followed by recovery. Albumin, marked trace.

Cells present. Polymorphonuclears = 82 %. Lymphocytes = 18 %.

(*e*) Pneumonia and rickets. Few degenerated cells. *Culture.* Sterile.

3. *Acute Gastro-enteritis.* Three cases, with convulsions. No cells or organisms found in two. In one the fluid was blood-stained and contained but few leucocytes. *Culture.* Sterile.

X. In eight cases the deposit obtained by centrifugalizing the cerebro-spinal fluid yielded on evaporation numerous minute colourless rhomboid crystals. Their nature and pathological significance, if any, has yet to be proved. They may indicate the presence of a chloride or some other salt in excess of the normal.

The cases in which they occurred are as follows:—

1. *Cervical caries.* The fluid contained no albumin, cells or organisms.

2. *Tuberculous meningitis.* The fluid also contained scanty lymphocytes, but no tubercle bacilli were found.

3. *Cerebral diplegia,* with convulsions. The fluid was blood-stained and contained but few leucocytes, and the cultures proved sterile.

4. *Hydrocephalus.* Scanty leucocytes also present. No organisms found.

5. *Polio-encephalitis.* A few lymphocytes were also found, but no organisms.

6. *Pneumococcal meningitis.* A few degenerated polymorphonuclears and abundant pneumococci were present in the fluid.

7. *Whooping cough,* with convulsions. The fluid also contained a few degenerated cells. *Culture,* sterile.

8. *Post-basic meningitis.* Abundant cell deposit, meningococci in film preparations and pure culture.

The information derived from the examination of the cerebro-spinal fluid shows that, in the majority of cases, both from the positive and negative aspects, the operation of lumbar puncture provides a means of diagnosis of great importance.

It is another matter to decide whether it should be performed purely as an aid to diagnosis apart from its possible therapeutic value. The risk is apparently small, for no injurious effects ensued in the 140 cases collected in this paper. On the other hand this figure is not sufficiently high to lend great support to the claim that the operation though skilfully performed is devoid of serious consequences.

I have to express my indebtedness to members of the staff of the Hospital for Sick Children for kind permission to make use of the material derived from their cases for purposes of publication.

DESCRIPTION OF FIGURES.

FIG. 1. Lymph clot from cerebro-spinal fluid, showing tubercle bacilli stained by carbol fuchsin and methylene blue. Drawn under $\frac{1}{12}$ oil-immersion and 8 eye-piece. (From the same case as FIG. 3.)

FIG. 2. Cell deposit from cerebro-spinal fluid of a case of tuberculous meningitis, showing great excess of lymphocytes (97·5 %). Stained with Jenner's fluid. Drawn under $\frac{1}{12}$ oil-immersion and 4 eye-piece.

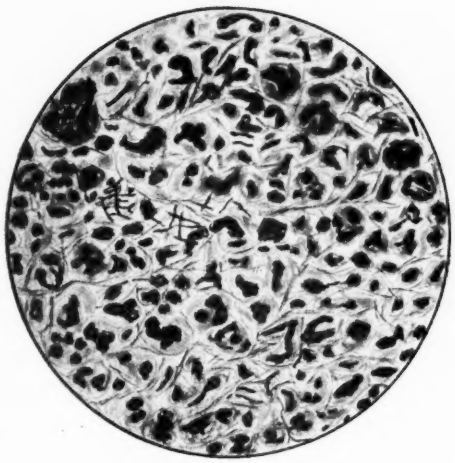
FIG. 3. Cell deposit from cerebro-spinal fluid of a case of tuberculous meningitis, showing abnormal excess of polymorphonuclears (71·3 %). Stained with Jenner's fluid. Drawn under $\frac{1}{12}$ oil-immersion and 4 eye-piece. (From the same case as FIG. 1.)

FIG. 4. Cell deposit from the cerebro-spinal fluid of a case of post-basic meningitis, showing normal excess of polymorphonuclears (in this case 65 %), and 35 % of lymphocytes; also many intra- and extra-cellular meningococci and a few colourless rhomboid crystals. Stained by Jenner's fluid. Drawn under $\frac{1}{12}$ oil-immersion and 4 eye-piece.

FIG. 5. Cell deposit from the cerebro-spinal fluid of a case of pneumococcal meningitis, showing the normal excess of polymorphonuclears and also a fair number of pneumococci. Stained with Jenner's fluid. Drawn under $\frac{1}{12}$ oil-immersion and 4 eye-piece.

FIG. 6. Crystalline deposit from the cerebro-spinal fluid of a case of pneumococcal meningitis, showing, in addition to the crystals, many pneumococci and a few degenerated leucocytes. Stained by Gram's method and eosin. Drawn under $\frac{1}{12}$ oil-immersion and 4 eye-piece.

I.



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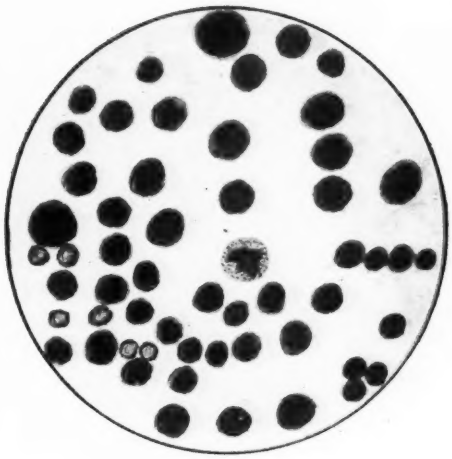

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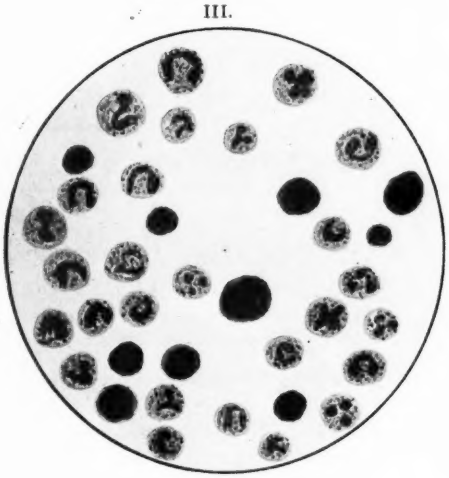

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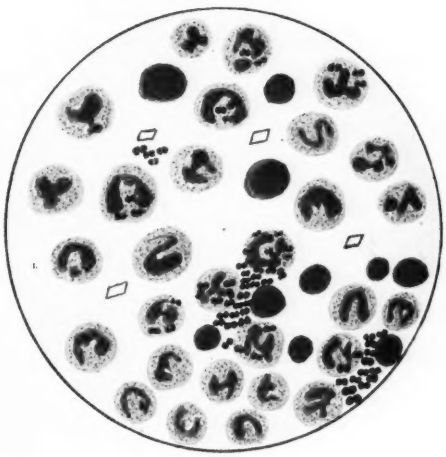

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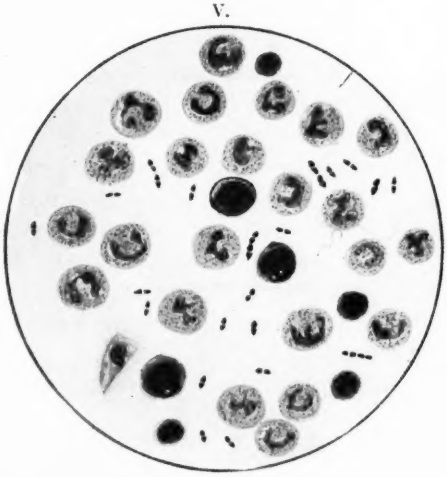

VI.

A STUDY OF CERTAIN REFLEXES IN SCARLET FEVER[1]

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For some few years the conditions of the reflexes in diseases other than those of the nervous system have attracted the attention of many observers both in this country and abroad. The reflexes of scarlet fever, however, have been little studied.

In the present paper, which is based on 175 cases of scarlet fever which have recently been under my care at the North Eastern Fever Hospital, I propose to consider, first, the plantar reflexes in scarlet fever, and, secondly, their relation to the abdominal and cremasteric reflexes and knee-jerks in the course of that disease.

The plantar response was the first reflex, at least in this country, to receive attention from clinicians. Todd,[2] in his lectures on the nervous system, published in 1854, constantly calls the attention of his hearers to the excessive and involuntary contraction of the foot muscles, in response to slight stimulation. The knee-jerk and the abdominal reflexes are not mentioned either by him or by his contemporaries.

Marshall Hall,[3] in his book entitled *Diseases and Derangements of the Nervous System*, lays equal stress on the plantar reflex, and further describes, in a case of hemiplegia, the abnormal extensor response, which more than fifty years later was described by, and named after, Babinski. The sentence taken from the edition of 1841 reads as follows: 'On tickling the sole of the left foot, the extensors of the toes, and especially of the great toe, were strongly contracted, still without consciousness.' He does not, however, contrast this form of response with flexion, the normal reflex of health.

Again, in the same work, he quotes Dr. Bailey, who, in the English edition of Professor Müller's *Physiology*, Vol. I, p. 721, writes as follows: 'The translator has under his care at the St. Pancras Infirmary, a woman, aged 53, recently attacked with hemiplegia and complete loss of sensation and motion, in whom pricking or even slightly touching the sole of the foot caused the foot to be retracted, and the toes extended, the patient being entirely unconscious of

[1] Abstract of thesis for the degree of M.D. in the University of Oxford.

[2] Todd, *Clinical Lectures on Paralysis, &c.*, 2nd ed., Lond., 1854.

[3] Marshall Hall, *Diseases and Derangements of the Nervous System*, Lond., 1841.

[Q. J. M., Jan. 1908.]

stimulus and movement.' He goes on to contrast this response with that of the sound side, in which stimulation of the sole, although clearly perceived by the patient, produced no such movements. The existence, but not the significance, of this abnormal response was, therefore, well known to clinical teachers .n the middle of the nineteenth century.

From this time up till 1876 little or no attention seems to have been paid to the superficial reflexes; in that year Rosenbach[4] called attention to the importance of the activity of the abdominal reflexes. Six years later, in 1882, Buzzard[5] published his *Clinical Lectures on Diseases of the Nervous System*, in which he states that the absence of the reflex from the sole is a very constant symptom of hysterical paraplegia, especially when associated with normal electrical contractility of the muscles of the lower extremity and normal tendon reflexes. It is interesting to note that these observations were confirmed by Crocq[6] more than twenty years after. This was the first attempt to show a relation between the superficial reflexes and the state of health of the nervous system. It followed shortly after the introduction of Westphal's knee phenomenon into English clinical medicine, and the importance of the latter's discovery no doubt distracted attention from the less striking, but equally interesting, reflex of the sole.

It was not till 1898, sixteen years later, that Babinski[7] published his now well-known paper in the *Semaine médicale*, and in the last nine years a plenteous crop of literature has grown round the subject of the cutaneous reflexes in general, and the plantar response in particular. The reflex was first of all studied in diseases which showed definite morbid changes in the central nervous system, but gradually its range of application has widened. In 1903 Kornilow[8] demonstrated the presence of Babinski's sign in a case of typhoid fever which did not show any other sign of pyramidal involvement. In 1906 J. D. Rolleston[9] confirmed Kornilow's results by finding Babinski's sign in 4 out of 45 cases of typhoid fever. Extension only lasted for a few days, and was then replaced by flexion.

In November, 1905, Kiroff[10] examined the reflexes in several severe cases of scarlet fever; in 7 of which there were either meningitis or signs and symptoms rendering the diagnosis of meningitis probable. He found that Babinski's sign occurred in 17 of these cases, in 10 of which death supervened.

The same author made a similar examination of 3 severe cases of diphtheria, and found a positive Babinski in all three.

J. D. Rolleston[11] in a paper on 'Precocious Paralysis of the Palate in

[4] Rosenbach, *Arch. f. Psych.*, Berlin, 1876, vol. 6, p. 845.
[5] Buzzard, *Clinical Lectures on Diseases of the Nervous System*, Lond., 1882, p. 118.
[6] Crocq, *Rev. neurol.*, Paris, 1904, vol. 12, p. 1069.
[7] Babinski, *Semaine méd.*, Paris, 1898, vol. 18, p. 321.
[8] Kornilow, *Deutsch. Zeit. f. Nervenheilkunde*, Leip., 1903, p. 222.
[9] Rolleston, *Brain*, Lond., 1906, vol. 29, p. 99.
[10] Kiroff, *Rev. neurol.*, Paris, 1905, vol. 13, p. 1118.
[11] Rolleston, *Review of Neurol. & Psychiat.*, Edin., 1906, vol. 4, p. 612.

Diphtheria,' found Babinski's sign in 5 out of the 9 cases in which he examined the plantar reflexes. He agrees with Kiroff in finding this phenomenon associated with absent or very sluggish knee-jerks.

It will now perhaps be profitable to enumerate the conditions in which Babinski's sign occurs:—

1. Coarse lesions of the pyramidal system, e.g. disseminated sclerosis, hemiplegia from whatever cause, with the probable exception of hysteria, transverse lesions of the spinal cord, and tumours of the brain or spinal cord involving the lateral motor paths.
2. Lesions of the pyramidal system of less permanent character than those enumerated under the heading of 1. Under this heading are included epileptic convulsions, and the pressure of exudations due to meningitis.
3. In cases where there is actually, or where there may fairly be supposed to be, a general microbic invasion of the whole organism. Under the first heading, typhoid fever is the striking example: under the second, scarlet fever and chorea.
4. In conditions of poisoning, either from substances ingested or from toxines produced by faulty metabolism. Under the first heading are such drugs as scopolamine and strychnine. Under the second, rheumatoid arthritis, some acute auto-toxic psychoses, and the terminal stages of severe anaemias.

The conditions grouped under heading 3 will now be briefly considered. Kornilow[12] was the first to describe the occurrence of Babinski's sign in typhoid fever. His case showed no other sign of pyramidal involvement.

The extensor phenomenon in typhoid fever is frequently associated with loss of the abdominal reflexes, with ankle clonus and with loss or impairment of the knee- and ankle-jerks. Usually, according to J. D. Rolleston,[13] the extensor phenomenon is of very short duration—three or four days, and is soon replaced by flexion. He compares the extensor phenomenon with the condition of the abdominal reflexes which, as would be expected, are far more frequently affected, and for a longer period of time, than the plantar reflexes. His observations were made on material of considerably greater age than mine (48 of his cases being over ten years of age), and taking this into account, and the well-known frequency of the occurrence of ankle clonus in children suffering from enteric fever, his figures, 7·7 %, must be considered a very moderate estimate indeed.

In 1905, Kiroff[14] wrote that in certain cases of scarlet fever characterized by high temperature, marked eruption, delirium and signs either of, or closely resembling, meningitis, the plantar reflex was one of extension either bi- or unilateral. He found that the reflex became normal on the cessation of the fever

[12] Kornilow, *loc. cit.*
[13] Rolleston, *Brain*, Lond., 1906, vol. 29, p. 99.
[14] Kiroff, *loc. cit.*

and the subsequent relative calm of the nervous system. The cases of scarlet fever selected by Kiroff were of unusual severity, for out of 17 cases 10 died. Of 7 cases meningitis was present in 5, and probably present in the other two. In 4 cases endocarditis was present either alone or complicated by meningitis. In 2 cases broncho-pneumonia was present. In the cases where scarlet fever is complicated by meningitis, Babinski's sign must be explained by oedema of the pia mater and sub-arachnoid oedema. Kiroff points out that with the presence of Babinski's sign the plantar reflexes were often absent; and that towards the close, in the fatal cases, the extensor plantar reflex tended to disappear.

The researches of Poynton and Holmes[15] leave little doubt that in chorea there is a generalized microbic invasion, and quite recently Charpentier[16] has described a case of chorea in which unilateral plantar extension occurred. The patient was a female, aged twelve, in whom chorea supervened after an acute attack of rheumatic fever. The inco-ordinated movements were generalized, but those on the right side were predominant. All the reflexes, except that of the left sole, were normal. On the left side plantar extension occurred, and persisted from October, 1906, till December, 1906, when she was shown to the Neurological Society of Paris.

The condition of the abdominal reflexes in the acute specific fevers was first discussed by Sicard, whose paper is based upon the examination of 26 children suffering from typhoid fever. In 22 out of the 26 this reflex was absent or very notably diminished. The period of absence or diminution coincided with the febrile period, the reflexes usually appearing a day or two before the temperature fell to normal. Of the remaining 4 cases, in 2 the absence was of very passing duration, in 2 the reflexes were brisk throughout the whole course of the disease. The reflexes may be absent on one side only, and if so, the right more commonly fails to respond to stimulation. The activity of the supra-umbilical response may often remain unimpaired, while that of the infra-umbilical is totally abolished.

J. D. Rolleston[17] made a similar examination in 45 cases of typhoid fever. In 42 of these cases the abdominal reflex was affected to a varying degree, being completely lost in 31, impaired to a greater or less degree, short of absolute extinction, in 11 cases. The duration of absence varied from one to twenty-one days, the average being 6·5, but the length of time during which the reflexes were impaired in activity varied from three to eleven weeks. He points out that this phenomenon may be of considerable diagnostic value in cases of long-continued pyrexia in which nervous and acute abdominal diseases can be excluded.

In prognosis it is also of use, for its return and, *a fortiori*, its resumption

[15] Poynton & Holmes, *Lancet*, Lond., 1906, vol. 2, p. 892.
[16] Charpentier, *Rev. neurol.*, Paris, 1906, vol. 14, p. 1176.
[17] Rolleston, *Brain*, Lond., 1906, vol. 29, p. 99.

of normal activity indicates commencing convalescence, and often corresponds with lysis. Lastly a renewed bout of pyrexia in convalescence, if associated with a loss of the abdominal reflex, favours the diagnosis of relapse rather than other causes of pyrexia. His results were confirmed by Claude Ker[18] and coincide with those of Ortali.[19]

The Abdominal Reflex.

In this paper the abdominal response to cutaneous excitation is sub-divided into three separate reflexes, each being governed by different segments of the cord.

The sub-divisions are as follows:—

(1) Epigastric; (2) Supra-umbilical; (3) Infra-umbilical.

The epigastric reflex is evoked by stroking the side of the chest downwards from the nipple. The result is a drawing in of the epigastrium on the same side as that to which the stimulus is applied. The superior umbilical reflex is evoked by stroking the skin of the abdomen from the costal margin to the nipple line. The response consists in retraction of the belly above the umbilicus. The inferior umbilical reflex is elicited by stroking the skin of the abdomen from the umbilicus downwards towards the anterior superior iliac spine. The result is a retraction of the belly below the umbilicus. In the cases of scarlet fever to be described, the reflexes have always been elicited by stroking the skin lightly with a pen-holder. The importance of light stimulation has been demonstrated by Grainger Stewart.[20] According to this authority, a false reflex, analogous to the patellar tendon reflex is obtained if the oblique abdominal muscles are suddenly stretched by a too forcible stroke. This spurious abdominal reflex may be obtained in several spastic conditions where the true superficial abdominal reflex is lost. The attention of the patient has always been as far as possible distracted, so as to ensure relaxation of the abdominal walls.

Cremasteric Reflex.

Scant attention has been paid to this reflex, and but little has been written as to the causes of its absence. It is certainly the briskest reflex of childhood, but it is commonly regarded as being often absent or very sluggish in adult life. Steiner,[21] however, found it to be present in 90 out of 100 young soldiers, and that unilateral stimulation often produced a bilateral response.

In childhood it is excited by stimuli applied to quite remote areas. Thus

[18] Ker, *Practitioner*, Lond., 1906, vol. 2, p. 780.

[19] Ortali, Abstracted from the Gazz. degli Osped. in the *Review of Neurol. & Psychiat.*, Edin., 1906, vol. 4, p. 222.

[20] Grainger Stewart, *Lancet*, Lond., 1906, vol. 2, pp. 1209–11.

[21] Steiner, *Deutsch. Zeit. f. Nervenheilkunde*, Leip., 1904, vol. 15, p. 285.

minimal stimulation applied to the hollow of the plantar region calls forth a brisk response on one or both sides. Likewise a minimal stimulus applied to the skin of the abdomen is followed by a unilateral or bilateral response of the cremaster muscles. A stimulus greater than minimal, if applied to the external or internal regions of the leg, will in many cases elicit the cremasteric response.

In the 175 cases of Scarlet Fever enumerated hereafter, I have only found this reflex absent in one case. In another case of a child suffering from whooping cough and bromoform poisoning, this reflex was abolished on both sides for about three hours. It was the first reflex to reappear as recovery ensued.

Detailed Consideration of certain Reflexes in 175 Cases of Scarlet Fever.

In the following investigation the material studied was obtained from the hospitals of the Metropolitan Asylums Board, and as it is the custom of that board to transfer patients to convalescent hospitals, it has been impossible to follow the mild cases to their termination.

Owing to the nature of the plantar response in early youth, it has been necessary to exclude children under two years of age, and the incidence of secondary disease would also tend to obscure the issue and to make it doubtful which toxin was exercising its effects upon the central nervous system. Cases of scarlet fever complicated by measles or diphtheria have, therefore, been rigorously excluded. Examinations of the reflexes have, as a rule, taken place twice a week, but in some cases the reflexes were examined far more frequently, in some cases daily. It has been thought advisable to subdivide the cases according to the severity of the disease, into—(1) Mild; (2) Moderate; (3) Severe.

Under the heading of 'mild' are included all those patients in whom there is little or no constitutional disturbance, in whom the temperature is raised only one or two degrees, and in whom the en- and ex-anthemata are very slight. All cases with complications have been excluded from this group.

The class headed 'severe' comprises subjects who suffer from profound constitutional disturbance and high temperature, and those who present the train of symptoms justifying the diagnosis of septic scarlet fever. Such cases are characterized by much glandular enlargement, profuse rhinorrhoea and a characteristic coarse rash. Under this heading I have also grouped patients, who on admission have not been regarded as being severely ill, but who have at later periods developed complications causing great danger to life, such as pneumonia, nephritis and endocarditis.

The 'moderate' cases include those of average severity with slight constitutional disturbance attended by moderate degrees of pyrexia. All cases presenting complications not dangerous to life have been included in this division.

Of the 175 cases, 132 were classified as 'moderate', 20 as 'severe', and

23 as 'mild'. The two sexes are not quite equal in number, 100 being females and 75 males. The average age of the 175 cases was 7·08 years.

It is now proposed to discuss each group or division separately. The cases in each division showing the extensor type of plantar reflex are first considered; and secondly those who show either a normal flexor response, or no plantar reflex at all. The sex and age of the patients are first detailed, then the condition of the plantar reflexes is examined, and the duration of any changes in these responses is recorded. The condition of the abdominal reflexes and of the knee-jerk is then described, and finally a list of the complications occurring in each group is appended, and an account given of the state of the reflexes in each variety of complication.

Examination of the 20 *cases grouped under the heading 'Severe'.*

Of these 20 cases as many as 14, or 70%, showed the extensor type of plantar reflex. These 14 cases will now be considered in detail. Six of the cases were males, eight were females.

The average age for the males was 6·3, and for the females 6·4 years. The slight preponderance in favour of the females cannot be assigned to age, since, as will be shown later, the younger the patient the more likely is an extensor type of response to occur. Examination of the complications occurring in the males and females will show that the latter were afflicted with more severe forms than those of the stronger sex, and it is to this rather than to such a vague remark as the 'well-known instability of the female nervous system' that the increased nerve vulnerability must be attributed.

In all but 4 of the 14 cases, extension occurred on the first day of observation, which on the average was the third day of the disease, as judged by the appearance and history of the case on admission to hospital.

In the 4 cases mentioned above the normal flexor type of reflex preceded the onset of an extensor response by a widely varying limit of time, which in one case was 5 days, and in another 23. In some cases the onset of complications ushered in a change in the type of reflex activity, in others no such explanation was forthcoming.

In the majority of the cases the reaction was bilateral; in two only were unilateral responses obtained. The duration of the extensor phenomenon varied widely, but the average for the 14 cases was 24 days.

In 2 cases only were the knee-jerks absent, in one case up till the seventh, and in the other from the seventh till the twelfth day. In both these cases the abdominal and epigastric reflexes were entirely obliterated for varying lengths of time. The first of these cases was complicated by scarlatinal rheumatism and endo- and pericarditis; the second was a case of septic scarlet fever.

The epigastric and abdominal reflexes were found to be absent in 8 of the 14 cases which showed an extensor plantar reflex. Of these 8, 2 were males

and 6 were females. The average duration of absence of the abdominal and epigastric reflexes was 21 days.

From the above figures it may be concluded that—

(1) There is a general but by no means absolute correspondence between the plantar and abdominal reflexes or between the plantar and abdominal reflexes on the one hand, and the presence or absence of the knee-jerk on the other.

(2) The various reflexes are affected in the following order:—(i) Plantar, 70%; (ii) Abdominal, 57%; (iii) Knee-jerks, 14·2%.

(3) In the majority of cases, the epigastric and abdominal reflexes were simultaneously affected, but in one case the epigastric was affected eleven days before absence of the supra- and infra-umbilical reflexes was noted. In another case both abdominal and epigastric reflexes were simultaneously affected, but the epigastric returned before the supra- and infra-umbilical.

Complications of various kinds occurred in 13 out of the 14 cases.

It is noteworthy that the cases complicated by endocarditis showed more impairment of reflex activity than the cases complicated by adenitis, rheumatism, nephritis, broncho-pneumonia and rhinorrhoea.

Examination of the reflexes in the 6 'severe' cases not showing extension.

These cases comprise 5 females and 1 male, whose ages average 6·9 years, which is, if anything, slightly higher than that of the severe cases in which a definite plantar extensor response occurred.

In two of these cases there was no alteration in the plantar reflexes, flexion persisting throughout the whole period of observation. The first of these was a female, aged 6, in whom there was high fever and much constitutional disturbance; in this case the plantar reflexes were normal throughout, but the abdominal reflexes were absent for 10, and the knee-jerk for 3 days. The second case was a male, aged 3, in whom there was severe vomiting that persisted for 3 days. In this subject also the plantar reflex retained its integrity, but the abdominal and epigastric reflexes were absent for 8 days.

In the remaining 4 cases no plantar reaction could be obtained for varying intervals of time. In 2 cases the plantar response was entirely absent on the admission of the patient to hospital, the one case being admitted on the third, the other on the second day of the disease. In the first of these cases the normal plantar response returned on the sixtieth day from the commencement of the illness.

The epigastric and abdominal reflexes were absent in all but one of these cases. In the one case in which these reflexes remained intact there was a period of no plantar reaction lasting for 18 days.

The average duration of absence of the epigastric and abdominal reflexes in

the 6 cases given above was 16 days; the 14 cases which showed extension gave an average duration of absence of 21 days.

The knee-jerks were found to be absent in one case only, and in that the plantar response remained unchanged, but the abdominal and epigastric reflexes were abolished.

If the 20 severe cases are grouped together it will be found that in all but 2 cases there was an alteration in the plantar reaction, either in the direction of complete change of type of response or complete suppression.

The epigastric and abdominal reflexes were totally abolished in 13 of the 20 cases. In 2 out of these 13 cases there were no changes from the normal in the plantar responses; of the 7 cases in which the epigastric and abdominal responses were normal, in 6 the plantar reflex was of the extensor type, in 1, of the flexor.

In 11 cases, then, a change in the abdominal reflexes was associated with an alteration in the plantar response, or, to put it in another way, of the 18 cases in which an alteration in the plantar response was found, in 11 the abdominal reflexes were completely suppressed.

It may be concluded, then, that generally, but by no means always, alteration of the abdominal reflexes accompanies change in the plantar responses.

Examination of the 23 *'mild' cases.*

As in the preceding section, so here, the cases showing an extensor type of response are first considered, then those in which the plantar response is either normal or altogether absent. Of the first variety there are only four.

The average age of these 4 cases was 7·1 years. The duration of the extensor response in these cases was 11·7 days, i. e. less than half that of the severe cases.

In only one of these 4 cases was the epigastric and abdominal reflexes absent; the duration of absence was 18 days. In all 4 cases the knee-jerks and the cremasteric reflexes were brisk.

Examination of the remaining 19 *cases in which extension did not occur.*

The average age of these 19 cases was 7·3 years, which is about the same as that of the 4 cases showing an extensor response. It is interesting to note that whereas the extensor cases above 7 years of age are only 50% of the whole, in those which show flexion or no plantar response the percentage is 78·9. So here again, as in the severe cases already considered, extension is more likely to supervene in the younger cases.

In 11 of the 19 cases the normal character of the plantar response, namely flexion, persisted throughout. The last day of observation on the average was the thirty-first of the disease. In these mild cases, then, 50% showed no alteration in the plantar response, which contrasts surprisingly with the small

percentage of 10 which retained the normal plantar reflexes in the cases classified as severe.

In one case no plantar reaction could be obtained throughout the whole period of observation, although the abdominal and epigastric reflexes were brisk.

In 7 of the mild cases flexion occurred, followed by no plantar reaction for a varying interval of time, the average for the 7 cases being 10 days. In one of these cases the period of no reaction, which lasted for a week, was followed by a return to the normal response. In 7 out of 19 cases the epigastric and abdominal reflexes were absent. In one case the epigastric portion of the abdominal response was the only reflex to be affected, in another the left inferior umbilical resumed its normal activity 14 days before the epigastric and the superior and right inferior umbilical reflexes.

Conclusions.

(1) The reflexes are much less frequently affected and for a much shorter period of time in the mild than in the severe cases of scarlet fever.

(2) In none of the mild cases were the knee-jerks or cremasteric reflexes affected.

Examination of the Reflexes in 132 *cases of Scarlet Fever of 'moderate' severity.*

These 132 include 80 females and 52 males. The average age of these cases was 7 years. Following the plan previously adopted the cases will be considered according to the character of the plantar response shown.

The distribution is as follows :—

A. Cases showing an extensor plantar response (66 cases), and *B*, cases showing a flexor response (61 cases), or no plantar response (5 cases).

It will now be well to contrast the ages of the cases showing plantar extension on the one hand, and those showing flexion and no plantar reaction on the other.

My figures show that age favours the occurrence of the normal response, as only 36·3% of the *A* cases are above 7; while as many as 50% of the *B* cases surpass that limit. It is interesting to note that no case above 20 showed an extensor response. The sexes were equally affected, no preponderance being given to the females.

Extension was found to be present on the first day of observation in 56 of the 66 cases; in the remaining 10 it occurred later. It might be suggested that extension had occurred and given way to flexion, but this is improbable, as in the last ten cases the first observation was on the third day, if anything slightly earlier than the first observation in the 56 cases showing Babinski's sign.

In 3 of the 10 cases an explanation is forthcoming, in the fact that the

change in the type of plantar response is contemporaneous with the supervention of some complication. In the 3 cases mentioned, the complications were acute endocarditis, nephritis and scarlatinal arthritis. In the remaining 7 cases no such explanation is available.

In 48 cases Babinski's sign was present on both sides. In 18, it was unilateral. In the latter, the average duration of the extensor response was less by nearly two days than the former, who showed the phenomenon on both sides.

The duration of the extensor plantar response in the cases of moderate severity averages out as only 10·7 days, which is less than half of the number seen in the most dangerous cases, and is actually less than that recorded for the mild. But the number of the mild cases showing Babinski's sign was so small that a fairer idea is obtained by having recourse to expression by percentages. If this method be adopted it is found that for the mild cases the percentage of cases showing a duration of plantar extension of over two weeks is only 8·6, while in the moderate it is 27·2. Further extension never occurred after the second week in the mild, while in the moderate cases it persisted after the third week in 9 cases. In only 7 of these 66 cases did extension persist throughout the whole period of observation.

It is interesting to note that in nearly half the cases there was found absence of the plantar response, there being either total abolition or limitation of the response to the hip muscles.

In 8 of the 30 cases described which had no plantar reaction a brisk response was obtained in the hip muscles. This limited form of response persisted in these 8 cases until the last day of observation, some 14 days later. The absolute suppression of the plantar reflex persisted for 24 days, and the partial reflex confined to the hip muscles was then obtained up to the last day of observation, which on the average was the fortieth of the disease.

In 61 out of the 66 moderate cases showing extension, the abdominal and epigastric reflexes were investigated. In 29 they were active throughout, in 32 they were absent for varying intervals of time, the average being 16·4 days, which is nearly 7 days longer than the average period of extension.

There was no absolute correspondence between the period of extension and the length of absence of the abdominal responses. In 27, both epigastric and abdominal reflexes were equally affected. In 5, however, the epigastric alone were affected. In one or two cases it was noted that the inferior umbilical returned before the superior umbilical and epigastric reflexes. In none of these cases were the knee-jerks ever found absent.

Examination of the reflexes in 61 *cases of Scarlet Fever of moderate severity in which an extensor plantar reflex did not occur.*

It has already been stated that the age was higher in the cases showing flexion than those in which an extensor response occurred. The duration of the period of no plantar reaction varied within fairly wide limits, but the average

was 15 days. It is difficult to explain why a more or less prolonged period of abolition of the plantar response should occur in some cases and not in others. It cannot be explained by age, by severity of the disease, or by an undue percentage of complications. As a matter of fact, the cases which showed no alteration in their plantar response *showed a higher percentage of complications.*

In 14 of these 40 cases a special note was made about the activity of the hip muscles. In 9 of these cases the hip and plantar muscles were contemporaneously affected, and resumed activity at the same date. In the other 5 the hip muscles resumed their activity before those of the sole, the average period of absence of response in the former being 14 days; in the latter, as has been mentioned above, 15 days. It may be concluded from the observation of this and other groups that the hip response returns before that of the sole.

The epigastric and abdominal reflexes were examined in all the 61 cases. In 18 they were found totally abolished for varying periods, the average for the 18 cases was 21 days. In 5 cases, not included in these 18, the abdominal responses were occasionally absent, so in 23, or 37 %, there was impairment in the activity of these reflexes. Referring back to the results obtained for the cases of similar severity, but showing Babinski's sign, we find that in 48 % of the cases there was total abolition of the belly reflexes.

If the cases with a normal plantar reflex throughout are compared with those in which the plantar reflex was temporarily suppressed, as regards the total abolition of their abdominal reflexes, it will be found that the percentage of the former is only 18 as compared with a percentage of 36 belonging to the latter. So here again a rough correspondence is shown between the condition of the plantar and abdominal reflexes.

Consideration of the 5 moderate cases of Scarlet Fever in which on admission no plantar response could be obtained.

These 5 cases include 3 males and 2 females, their average age being 6 years.

In all but one of these cases no plantar reaction could be obtained throughout the whole period of observation, which extended up to the twenty-ninth day of disease; in one case on the thirty-seventh day of the disease there was a return to the normal response of flexion. In all but one of the cases the epigastric and abdominal reflexes were totally suppressed, the average duration being 18 days. With the exception of one case, in which the epigastric response was abolished for 11 days longer than the abdominal, these reflexes were equally and contemporaneously affected.

In one case, the only example in the whole series of 175, the cremasteric reflex on both sides was abolished. In no case were the knee-jerks absent or ankle clonus present.

An examination of the complications occurring in the 132 *cases of Scarlet Fever of moderate severity.*

Among these 132 there were 39 cases in which complications of various kinds were noted. The complications were distributed among these 39 cases as follows:—

Endocarditis, 9 cases; Nephritis, 7 cases; Adenitis, 8 cases; Otorrhoea, 8, in 3 of which there was also glandular involvement; Rheumatism, 3 cases; Rhinorrhoea, 3 cases; Albuminuria, 1 case.

Of these 39 cases, plantar extension was found to occur in 18, flexion in the remaining 21.

In these cases also it was again clearly manifest that those subjects who are attacked with endocarditis give evidence of the most marked nerve involvement, and that although there was a rough correspondence between the condition of the plantar and abdominal reflexes, this was by no means always the case. Again, the duration of the phenomenon of plantar extension was usually considerably less than the period of abolition of the abdominal reflexes. On the other hand, the period of no plantar reaction was usually greater than the period of abolition of the abdominal reflexes.

Conclusions.

(1) In many cases of Scarlet Fever, the normal plantar response of flexion is temporarily replaced by extension.

(2) The severer the case, and the younger the patient, the more likely is this change to occur, and generally speaking, the severer the case the longer the duration of this phenomenon.

(3) In a few cases all forms of plantar response were abolished.

(4) In a large number of cases, whatever the type of response first obtained, there was an interval of varying duration, in which the plantar reflexes were absent. In some cases there was complete absence of this reflex, the muscles of the hip normally concerned in this response being as inactive as those of the foot. In others the hip reaction was brisk, while the muscles of the foot failed to respond.

(5) The epigastric and abdominal reflexes are also affected, and, as in the case of the plantar response, so here, the more severe the attack the greater is the liability of their being affected, and the longer is the duration of any such affection.

(6) The epigastric and abdominal are less frequently affected than the plantar reflexes.

(7) Usually the epigastric and abdominal reflexes are contemporaneously affected, if anything the epigastric is more likely to show diminished activity or abolition than the supra- or infra-umbilical response.

(8) The cremasteric response is the briskest reflex of early youth, and is the least likely of all reflexes to be abolished.

(9) The knee-jerks were found to be absent in only 3 cases. All these three cases belonged to the class labelled 'severe'.

(10) Subjects attacked with endocarditis showed more derangement of their reflexes than those afflicted with other complications of Scarlet Fever.

THE EXTRA-SYSTOLE: A CONTRIBUTION TO THE FUNCTIONAL PATHOLOGY OF THE PRIMITIVE CARDIAC TISSUE

By JAMES MACKENZIE, M.D.

Part I.

Irregularities of the heart are of such frequency, and their presence so readily recognized by both patient and physician, that it is necessary clearly to recognize their meaning and significance. Until a few years ago, their nature was shrouded in obscurity, and in consequence the mystery regarding them in a great measure oppressed both patient and physician.

The fact that in some instances irregularity is of serious import has led to the supposition that all irregularities are signs of some grave mischief. In consequence of this, many patients are subjected to unnecessary fears, made to carry out elaborate methods of treatment, and to have imposed upon them burdensome and unnecessary restrictions. In addition direct injury is done to many individuals in the matter of life insurance, when they are rejected, or have imposed upon them the penalty of higher premiums in consequence of the complete misunderstanding of the significance of the irregularity.

The advance that has been made in the knowledge of this subject within recent years practically constitutes a revolution. By the combined efforts of clinicians and experimental physiologists, what was recently a complete mystery is now one of the best understood matters in the whole science of medicine. Not only has the scientific aspect been worked out, but by following individual cases for years, and observing how people with irregular hearts have borne the stress of life, a clearer conception has been obtained of the bearing of the different irregularities on the future history of patients.

There are three main circumstances which have combined to throw light on irregular action of the heart, viz. the experimental discoveries of the nature of the functions of the heart muscle, the application of graphic records of the jugular pulse to the interpretation of heart irregularities, and the discovery of the remains of the primitive cardiac tube in the mammalian heart, and its physiological significance. Although these are the main circumstances that have led to our present knowledge, yet much light has been thrown on the subject by experimental and clinical inquiries into other features of the heart's action, so much so indeed, that an inquiry into such an apparently simple

[Q.J.M., Jan. 1908.]

phenomenon as the extra-systole in man reveals the most varied actions of the heart in health and in disease, and gives a remarkable insight into the functional pathology of the heart.

The experimental production of extra-systoles. The starting-point of our knowledge of the extra-systole was when Marey demonstrated that in a rhythmical-beating frog's heart, the ventricle, during certain phases of the cardiac cycle, responded to an electrical stimulus. After this 'extra contraction', the ventricle remained quiescent for a longer period than it did after a normal contraction—the so-called compensatory pause. It was found that the irregular period, i.e. from the beginning of the ventricular contraction before the extra contraction till the end of the compensatory pause—was equal to two normal cardiac cycles (Fig. 1). Engelmann explained the reason of this by showing that the sinus and auricle pursued their normal rhythm, and that the stimulus from the auricle, after the ventricle had been artificially stimulated, failed to excite a ventricular contraction—the ventricle was 'refractory', and remained quiescent until the next normal stimulus came down from the auricle. Cushny

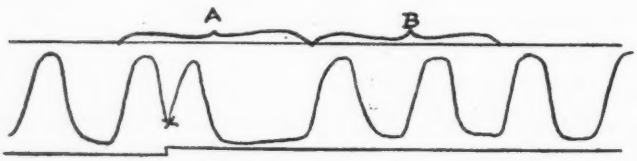

FIG. 1. Tracing of the movements of the ventricle of a frog. At × the ventricle was artificially stimulated and a contraction resulted followed by a long pause. The irregular period (A) is exactly equal to two normal periods (B). (After Marey.)

and Matthews and Wenckebach independently of these authors, found that the laws governing the production of the extra-systole in the frog's heart were, with slight differences, applicable to the mammalian heart, a result confirmed by H. E. Hering. Wenckebach, Cushny, and Hering applied the knowledge thus obtained to the interpretation of the irregularities in man.

The jugular pulse. The movements in the jugular vein had been graphically recorded by Bamberger and Marey in 1863, and the subject was greatly advanced by the researches of Potain, Riegel, François Franck, Gerhardt, and others. In working at the venous pulse in 1892, I used it as a means of interpreting irregular action of the heart, and in 1894, I published some results showing that the auricle could contract before its time, and that the ventricle also could contract prematurely at the same time as the auricle—in other words, these irregularities were what is now recognized as auricular and ventricular extra-systoles.

I continued this work, and published a fuller account in a book on the Pulse in 1902. Since then this method of inquiry into the irregular heart has been widely adopted, and O. Nicholson, H. E. Hering, Gerhardt, John Hay,

Ritchie, Pan, Wenckebach, Morrow, Hirschfelder, and others have not only added to our knowledge of the subject, but have shown what a wide field for clinical investigation has been opened up.

As the registration of the movements of the auricle gave the key for the interpretation of the extra-systole when it was experimentally produced, so the registration of some movement due to the auricle in man gives us the key to the recognition of the extra-systole and its various forms. For this purpose the jugular pulse affords the best means of recording the contraction of the auricle. In a tracing of the jugular pulse even when there are but faint movements in the veins, a series of waves is found whose significance, as a rule, can be easily recognized. When the radial pulse is taken at the same time as a standard, the relation of the various waves to the radial pulse gives the clue to the meaning of the waves in the tracing from the neck. We generally

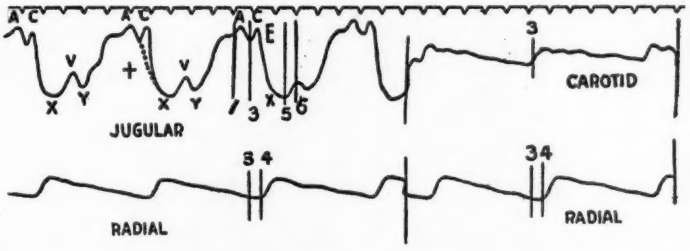

FIG. 2. Simultaneous tracings of the jugular and the radial pulses in the first part of the tracing and of the carotid and the radial in the latter part. The jugular pulse is of the auricular type. *a*, auricular wave; *c*, the carotid wave; *v*, the ventricular wave; *x*, the auricular depression; *y*, the ventricular depression. These letters have the same significance in all the other tracings.

find in the neck tracing a small wave due to the impact of the carotid pulse, and we recognize it by its constant relationship in time to the radial. As the wave that travels down the arm to the radial takes up some time, we find that the radial pulse appears generally one-tenth of a second behind the carotid. (Space between downstrokes 3 and 4, Fig. 2.) When, therefore, we want to find the carotid wave in the neck-tracing, we seek a wave one-tenth of a second before the radial pulse. When this is found, the interpretation of the other waves is usually very easy—thus a wave found immediately preceding is undoubtedly due to the systole of the right auricle (*a* in all the tracings), while a wave (*v*) following it, is due to the storing up of blood in the auricle and veins during the ventricular systole, its disappearance being due to the blood passing into the ventricle when the tricuspid valves open (downstroke 6 in all the tracings).

Position and function of the remains of the primitive cardiac tissue. The usual description that an extra-systole is due merely to the premature contraction of an auricle or a ventricle, leaves a great many features unexplained. Looking merely at the records of the contraction of auricle and ventricle, this

explanation is quite correct, nevertheless it gives a false idea as to the place of origin of the stimulus for contraction, an idea fostered by experimentation where extra-systoles can easily be induced by stimulation of the auricular and ventricular walls.

The fuller knowledge lately acquired as to the tissue in which the stimulus for contraction arises and is conveyed to auricle and ventricle, gives us the means of explaining a great many arrhythmias, and more particularly the extra-systoles.

The primitive heart is a tube, part of which in the course of development becomes differentiated into auricles and ventricles. In the mammalian heart the structure had been lost sight of till Kent and His, junior, discovered a portion

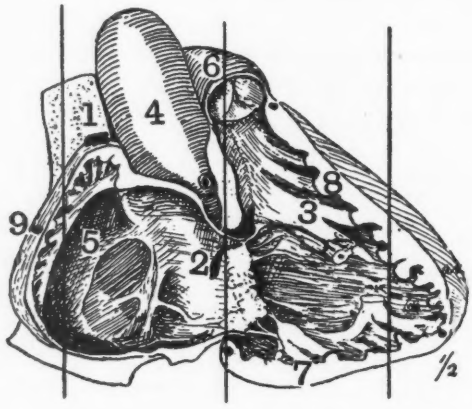

FIG. 3 shows the septal wall of the right auricle and ventricle of a human heart. 1. Superior vena cava above the sino-auricular node. 2. Auricular canal above the base of the septal cusp, where the *a–v* node is indicated with the *a–v* bundle running from it. 3. Moderator band, at the junction of the infundibulum and the sinus of the right ventricle, indicating the position of the right septal division of the *a–v* bundle. 4. Aorta. 5. Right auricle below the superior caval orifice and the taenia terminalis. 6. Pulmonary artery. 7. Diaphragmatic wall of the right ventricle (Keith).

of it in a narrow bundle joining auricle and ventricle. Within recent years Tawara has more fully investigated the matter, and has shown that this bundle starts in the auricular wall near the opening of the coronary sinus from a bulbous swelling (the auriculo-ventricular node). In Fig. 3 this node is shown at 2, and from this node a black thread is seen passing into the ventricular septum to 3, where the course of the branch of the auriculo-ventricular bundle to the right ventricle is shown. The bundle to the left ventricle branches off above the part marked by 3. In both ventricles the bundle breaks up into numerous fine threads that are distributed to the muscular wall. The histological constitution of the auriculo-ventricular node and main part of the bundle is very different from that of the branches and the filamentous threads

into which it breaks. The tissue of the node is made up of fine, pale, thin, branching fibres with faint striation intermingled with connective tissue fibres, whereas, in the human heart, the main branches and terminal filaments are made up of larger cells which resemble somewhat, and are of the same nature as the Purkinje fibres of the sheep's heart. Wenckebach, remarking that the starting-point of the heart's contraction was mainly near the mouth of the superior vena cava, conceived the idea that the remains of the sinus might be found here. He himself found certain muscular bands connecting the vein with the auricle, which suggested the possibility of these being the means of conduction between sinus and auricle. Keith and Flack made a careful investigation of this region in a number of different animals, and found a node of tissue there remarkably like that found by Tawara in the auriculo-ventricular node. Into this node of tissue (shown under 1 in Fig. 3), called by Keith the sino-auricular node, branches of the vagus and sympathetic nerves have been found to penetrate. As it possesses the most primitive structure of the remains of the sinus venosus—the part in which the heart's contraction starts in the lower animals—it is reasonable to assume that it is the starting-place in the mammalian heart. As in the dying heart independent pulsations can be seen starting at the pulmonary veins and coronary sinus, it can be assumed that these, which are also derivatives of the sinus, possess the primitive power of originating contractions, although no specialized muscular tissue has as yet been found in these parts. It will be seen in Fig. 3 that there is no connexion shown between the sino-auricular node and the auriculo-ventricular node. Whether such a connexion exists apart from the ordinary auricular tissue has not been determined.

The primitive cardiac tube carries on its work on account of its inherent functions, the most striking of these functions being its power of originating a stimulus for contraction, its power of conveying the stimulus from fibre to fibre, and its power of contraction.

It is reasonable to assume that the functions inherent in the primitive cardiac tube persist in the modified remains, except when more recently developed parts have taken on some special function. As the auricles and ventricles are specially differentiated portions of the primitive tube, and have taken on the function of contraction, the tube has ceased to act as a contractile agent. There is every reason to suppose that it still retains its place in the economy by reason of its possessing functions necessary to the due performance of the heart's work. The experiments demonstrating that this auriculo-ventricular bundle conveys the stimulus from the auricle to the ventricle is absolutely conclusive. That this primitive tissue still retains its functions of initiating the contraction is quite conceivable, and the assumption that it does so renders easy of explanation a great many facts hitherto inexplicable. In this paper the interpretation is based on the supposition that the extra-systoles arise in the primitive tissue—a supposition which has occurred to Kraus, Wenckebach, Hay, Ritchie, Morrow, and doubtless to many others.

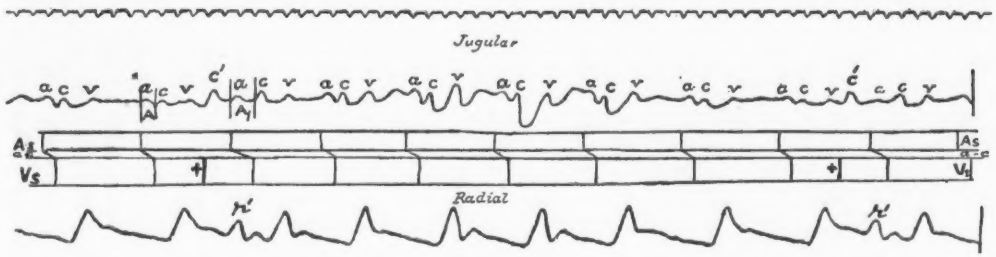

FIG. 4. Simultaneous tracing of the jugular and radial pulses, showing the interpolation of ventricular extra-systoles (c', c' and r', r') represented in the diagram by the downstrokes + +. The downstrokes in the space *As* represent the auricular waves (a) in the jugular, and the downstrokes in the space *Vs* represent the carotid waves c, and the slanting lines connecting them represent the a-c interval.

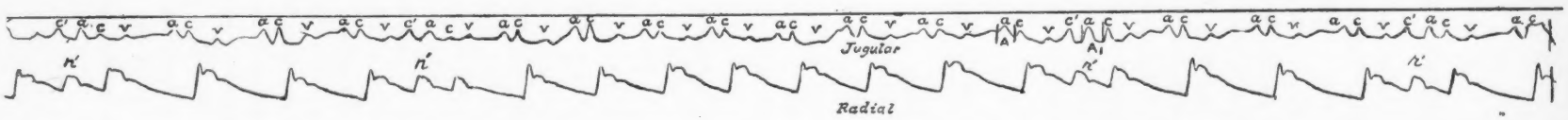

FIG. 5 shows the frequent occurrence of interpolated extra-systoles (c', r') with a prolonged a-c interval (A_1) after the extra-systoles (c').

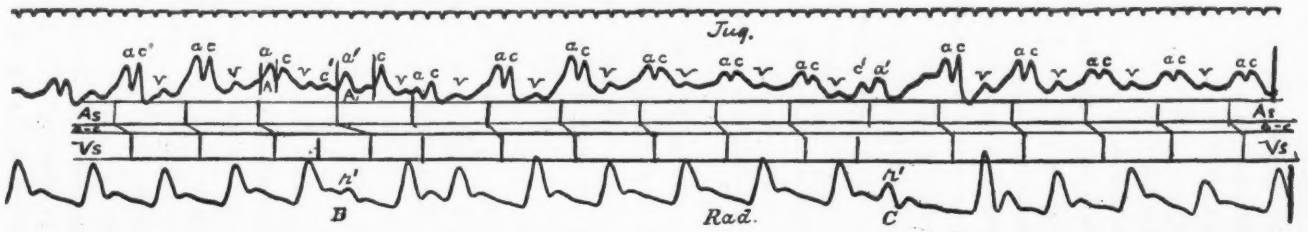

FIG. 6. During the irregular period B there is an extra-systole (r', c'). The auricular wave a' appears at the normal auricular interval, but the ventricular contraction following it is greatly delayed, the delay being shown in the diagram by a long a-c interval (space A_1). In the irregular period C the stimulus from a' fails to provoke a ventricular contraction.

Laws governing the functions of the heart muscle fibres. There are a few of the laws governing the functions of the heart muscle which it is necessary to bear in mind, as they afford the basis for certain important deductions. When the fibres of the heart contract, they do so with all the force of which they are capable at the time of stimulation, and this independent of the strength of the stimulus. That is to say, if the fibres are capable of responding to a stimulus, they do so with the same force whether the stimulus be a weak or a strong one.

Another feature is that the functions exercised are for a brief period annihilated after their exercise, and then gradually recover. Thus, immediately after contraction, the fibres cannot be stimulated, but when they begin to be capable of being stimulated to contract, they contract at first with a small force, and the force with which they contract becomes greater the longer the contraction is delayed—i. e. with longer rest, the force becomes greater. In like manner, if the function of conductivity be exercised, it takes some time to be restored. If stimulated too soon after being exercised, the fibres will either not respond, or they will do so by conveying the stimulus at a much slower rate. These remarks apply equally to the remains of the primitive cardiac tube, and to the muscular tissue of auricle and ventricle, and their recognition is necessary for the understanding of the results observed in cases of extra-systole, and other forms of irregularity.

Definition of the term 'Extra-Systole'. There are so many conditions that simulate extra-systoles, that a good deal of confusion exists in regard to what really constitutes an extra-systole, and it is therefore necessary to define the term. As the stimulus for contraction arises normally in the remains of the sinus venosus at the mouths of the great veins, and as the stimulus passes from these places to the auricle, then to the ventricle, so that there is normally a sequence of stimulation and contraction of sinus, auricle and ventricle, I would suggest that the term extra-systole should be limited to those premature contractions of auricle or ventricle in response to a stimulus from some other portion of the heart, but where otherwise the fundamental or sinus rhythm of the heart is maintained. The reason for this limitation I will explain when the nature of the extra-systole thus defined has been fully considered.

Ventricular extra-systoles. (The place of origin of ventricular extra-systoles is assumed to be in the *a–v* bundle beyond the *a–v* node.) The simplest form of extra-systole is that where a premature contraction of the ventricle is interpolated between two normal beats.

In Fig. 4 there are two small waves r' in the radial, which are due to extra-systoles of the left ventricle. In the tracing from the neck the waves *c* are due to the carotid, the waves *a* are due to the auricle, and the waves c' are due to the extra-systoles and correspond to r' in the radial. The diagram intercalated between the radial tracing and the tracing from the neck shows the relationship of the different events. The downstrokes in the upper compartment represent the beginning of the auricular systoles, and the downstrokes in the lowest compartment represent the beginning of the carotid pulse-beats, while

the slanting lines in the middle compartment represent the time between the beginning of the auricular and carotid waves (the *a–c* interval). In the cardiac cycles, apart from those in which the extra-systoles *r′* and *c′* occur, the ventricular contraction follows regularly on the auricular, and it is assumed that the sinus rhythm governs the contraction of the auricle. The extra-ventricular contractions are seen to start independently of the auricular contraction—that is, they are extra-systoles of the ventricle. The same features are to be recognized in Fig. 5, where there are four extra-systoles (*r′* in the radial, and *c′* in the jugular tracing); it will be seen that the auricular wave appears at regular intervals, and that the extra-systoles are interpolated between two normal beats.

In Fig. 6 there are two extra-systoles during the irregular periods B and C. In the jugular tracing it is seen that the carotid wave *c* follows the auricular wave *a*, but during the two irregular periods the carotid wave *c′* precedes the auricular wave *a′*, a fact brought out clearly in the intercalated diagram. We can prove that *c′* is due to the carotid, because it occurs at the same time after the preceding carotid wave that the radial beat *r′* appears after the preceding radial beat. The auricular wave *a′* appears at the normal auricular interval, and the auricle pursues its wonted regular rhythm while the ventricle is contracting prematurely and independently.

In the irregular period B, the interval between *a′* and the following *c* is greatly lengthened (space A,). The reason of this delay is shown in the diagram to be due to slower passage of the stimulus from auricle to ventricle—a fact of great importance, which will be dealt with in discussing the condition of the conductivity of the auriculo-ventricular bundle.

In the irregular period C, there is a much longer pause in the radial tracing after the extra-systole *r′*, and the intercalated diagram shows that this is due to the fact that the ventricle does not respond to a stimulus after *a′*. The difference between the irregular periods B and C is seen therefore to be due to the fact that in the irregular period B the ventricle responds to the stimulus from the auricular systole after the extra-systole, while in the irregular period C, the ventricle does not respond.

The irregular period C represents the most common form of extra-systole, and its appearance in graphic records is usually easily recognized by the presence of the long pause after the premature beat *r′*.

Thus Fig. 7 is a very characteristic example, and the intercalated diagram shows a regularly acting auricle and the premature and independent ventricular contraction with no response to the auricular systole after the premature ventricular contraction, which accounts for the long pause.

Simultaneous occurrence of the normal auricular systole and of the ventricular extra-systole. In the illustrations I have given of the ventricular extra-systole, in the jugular tracing the carotid wave *c′* was seen to precede the auricular wave *a′*. In these instances the normal rate was rather slow. In most instances, however, they fall together—the auricular contraction occurring

during the ventricular contraction. In consequence of this, the auricle cannot empty its contents into the ventricle, and hence a big wave is sometimes sent

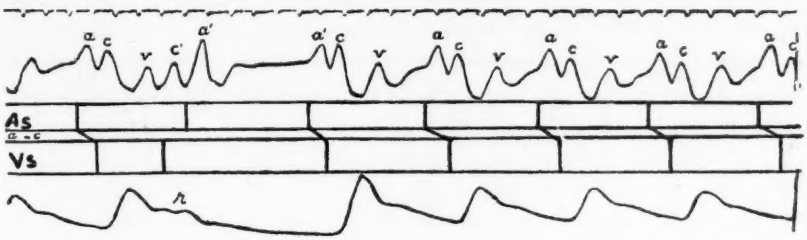

FIG. 7 represents a common form of ventricular extra-systole. There is a long pause after the extra-systole (r', c'). In the jugular tracing and in the diagram this is seen to be due to the failure of the stimulus from the auricle (a') to provoke a ventricular contraction.

into the jugular. In patients with a well-marked jugular pulse, this is readily recognized by the eye. In other cases the jugular pulsation is only to be seen when this big wave is sent back.

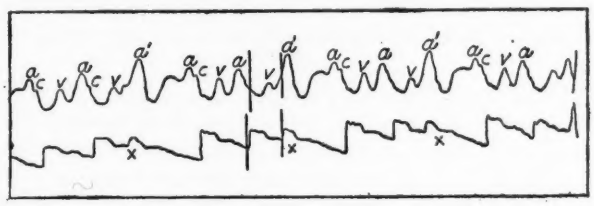

FIG. 8 shows the occurrence of three extra-systoles (× × ×) at the same time as the auricular waves a'.

In Fig. 8 the waves a and a' are due to the auricular systole and occur at regular intervals. The waves a' are, however, much larger than the waves a, and the reason for the increase in size is found in the fact that at that time the

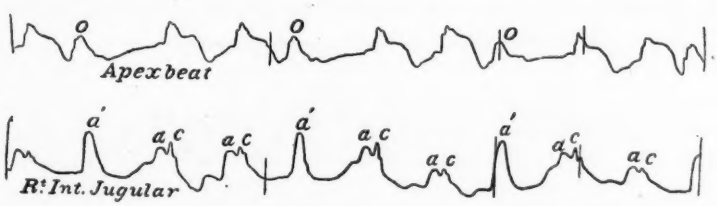

FIG. 9 shows premature contractions of the ventricle, o (extra-systoles), in the apex tracing, while in the jugular tracing are shown waves, a', due to the auricular systole occurring at the same time as the premature ventricular contractions.

ventricle was also in systole, causing the extra-systole. In Fig. 9 a simultaneous record of the apex beat and jugular pulse shows the premature contraction of the ventricle o at the same time as the large auricular wave a', so that here also

we have evidence of the simultaneous contraction of auricle and ventricle during a ventricular extra-systole. When there is a large jugular pulse the increased size of the auricular wave occurring during the extra-systole of the ventricle may not be so marked as in Fig. 10.

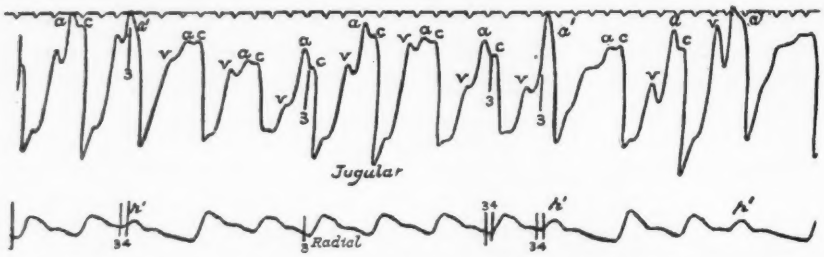

FIG. 10 shows three ventricular extra-systoles in the radial (r') while the auricle pursues its regular rhythm (a and a'). The downstrokes 3 and 4 represent the time of the carotid and radial pulses.

The auricular extra-systole. (The suggestion put forward here is that, in the production of the auricular extra-systole the stimulus arises in the primitive tissue incorporated in the auricle—the exact site being still undetermined.)

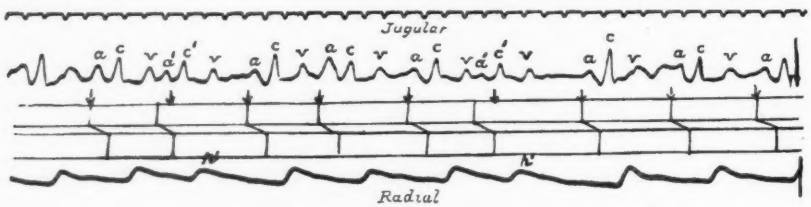

FIG. 11 shows auricular extra-systoles (a') followed by ventricular contractions (c', r'). The arrows in the diagram represent the sinus stimulation and the long pauses after the extra-systoles are seen to be due to the fact that the auricle did not respond to the sinus stimulation after the extra-systole.

When an extra-systole arises in the auricle, we may get a radial tracing presenting exactly the same features as when a ventricular extra-systole occurs, and it is only by a simultaneous record of the jugular pulse that the one can be

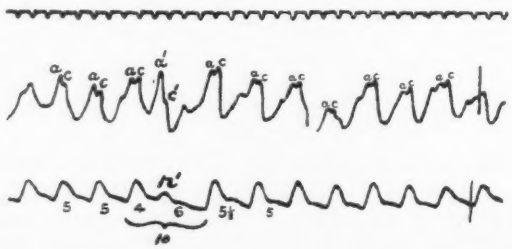

FIG. 12 shows an auricular extra-systole (a'). The numbers represent tenths of a second, and the irregular period is seen to equal two normal periods.

differentiated from the other. In Figs. 11 and 12, the radial pulse shows premature beats (r'), which can be readily identified as extra-systoles.

In the jugular tracings the carotid wave c' is preceded by an auricular wave a', and the only inference that can be drawn is that a' is due to an extra-systole of the auricle, which is followed by an extra-systole of the ventricle, producing the carotid and radial beats c' and r'.

In such instances as these the auricle is supposed to contract in reply to a stimulus from some source other than the sinus, and the long pause after the extra-systole is due to the fact that the stimulus from the sinus arising at its

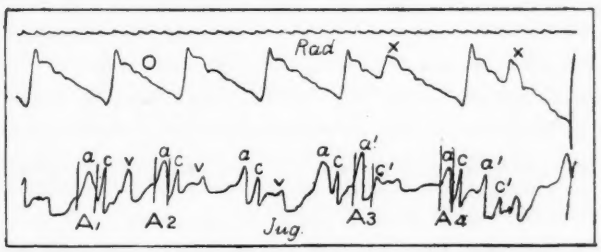

FIG. 13 shows two premature or extra-systoles of auricular origin (×). The waves c' in the jugular tracing occur at the same time as the small premature beats (×) in the radial tracing, and are therefore due to the carotid. These are preceded by premature waves a' due to the auricle. The interval a'–c' (space A_3) is greater than the average a–c interval (A_2), and is much greater than the following a–c interval (A_4).

normal time fails to provoke the refractory auricle to contraction. This is brought out in the intercalated diagram in Fig. 11, in which above the upper space are arrows representing the sinus stimulation. In the diagram it will be seen that there is no response to the sinus stimulation after the extra-systole, but that auricle and ventricle remain quiescent till the following sinus stimulation excites them to a contraction. In these two illustrations the irregular period is equal to two cardiac cycles, the explanation being obvious from the study of the

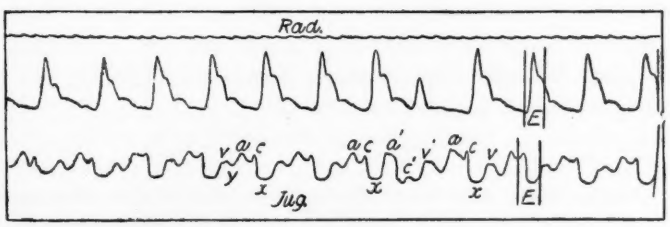

FIG. 14 shows an auricular extra-systole.

diagram in Fig. 11. In most cases of auricular extra-systole the irregular period is less than two cycles, as is shown in Figs. 13 and 14. The reason given by Cushny and Wenckebach, and usually accepted, is that the stimulus arising in the auricle passes back to the sinus and stimulates the sinus so that its stored energy is exhausted, and it begins to build up anew the stimulus material. As soon as it has again reached the excitable stage, it starts off the contraction. Thus in the diagram (Fig. 15), representing the events in Fig. 14, the stimulus

is represented coming down from the sinus to the auricle, but at the extra-systole (+) the stimulus is represented by an arrow passing back to the sinus, so that the sinus responds to the retrograde stimulation. After this premature stimulation, the sinus rests for a normal period, and starts off again at the normal rhythm. This irregular period, due to the auricular systole, is so frequently shorter than two normal beats that this is usually assumed to be the manner in which it is brought about. While it offers a plausible explanation it cannot be said in any sense to have been proved, and there are other

FIG. 15. Diagram representing the events in FIG. 14. The extra-stimulation at + is represented arising in the auricle, passing back and disturbing the sinus rhythm. Note the lengthened *a-c* interval after the auricular extra-systole.

possibilities which need consideration before it can be finally accepted. As however they are still speculative it would not be convenient to discuss them here.

The extra-systoles arising in the auriculo-ventricular node (nodal extra-systoles). So far the recognition of extra-systoles as ventricular or auricular has been comparatively easy. There is a third class which has hitherto not been sufficiently considered, and which, in my opinion, has been wrongly interpreted. The characteristic features of these extra-systoles is that auricle and ventricle contract prematurely and together. In Figs. 8, 9 and 10 it was

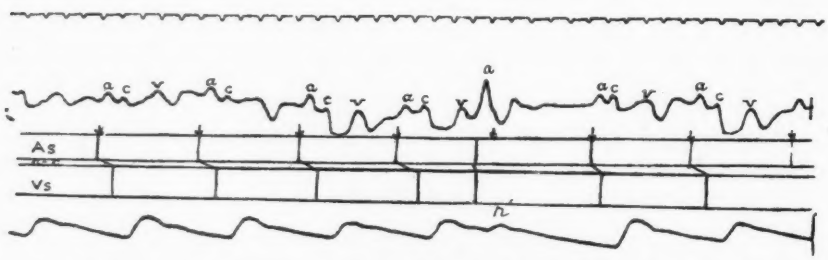

FIG. 16 shows a 'nodal' extra-systole, the auricular and ventricular systoles as shown in the diagram are premature and simultaneous.

demonstrated that auricle and ventricle contracted together, when the ventricular extra-systole appeared at the same time as the normal auricular systole. In these cases the auricle could be demonstrated to contract at its normal period. In another class of cases it can be demonstrated that both auricle and ventricle contract prematurely and together, the auricular wave appearing at the same time as the arterial pulse. Thus in Fig. 16, the auricular wave *a'* in the jugular appears prematurely, and obscures the appearance of the carotid pulse, the time of which can be ascertained by measuring the time between the extra-systole in the radial pulse, and the preceding beat. That the auricle did

not contract at its normal time is evident by the absence of any wave at the time of the arrow during the irregular period, which is the time when it was due. Here then we have evidence that both auricle and ventricle contracted prematurely and simultaneously. In the ventricular and auricular forms no difficulty is found in recognizing that the extra-stimulation must have affected either one chamber or the other, but in this form we have to consider where a stimulation could arise that would at once affect both chambers. If all the possibilities be considered, we are driven by a process of exclusion to attribute the source of this stimulation to the tissue that joins auricle and ventricle, and almost to a certainty to that portion described as the auriculo-ventricular node (2, Fig. 3). This will be brought out more clearly in the later discussion.

In many cases it is difficult to tell whether the stimulus producing the extra-systole arises in the ventricle at the same time as the normal auricular systole, or whether they have contracted together in response to an abnormal stimulation. In the latter case the abnormal stimulation affects the auricle at the same time that the normal was due, so that we do not get the proof of the premature contraction of the auricle. My reason for this suggestion is that sometimes we meet with a variety of extra-systoles in the same patient, indicating that at one time the auricle is prematurely stimulated, at another time the ventricle, and again both ventricle and auricle together. This is well seen in Fig. 17, where three forms of extra-systole occur.

The wave a' in the irregular period C is manifestly a premature or extra-auricular systole followed by a premature carotid wave c', which corresponds in time to the extra-systole in the radial tracing. In the irregular period B, the auricular wave a' appears at its normal interval, but in the radial tracing there is seen an extra-systole which appears at the same time as the wave a'. This is undoubtedly a ventricular extra-systole. In the irregular period A and D the conditions are not the same. The wave a' here has quite a different appearance from what it has in either B or C, being broader at the top. It is difficult to be certain whether it appears before the normal auricular systole was due, as there is a little sinus arrhythmia—the pulse periods not being of equal duration. The absence of the extra-systole in the radial does not imply that the left ventricle did not contract, for, as we shall see later, the ventricle may contract so feebly that a pulse-wave does not reach the wrist. That this view is probably correct can be inferred from the nature of the extra-systoles that occurred from time to time in the patient. Thus the typical auricular extra-systole in Fig. 14 is from the same patient. Fig. 18 is also from the same patient, and shows two irregular periods in which the large wave a' appears before a normal auricular systole was due. From this I suggest that this wave is of the same nature as that of a' in the irregular periods A and D, Fig. 17—namely, due to a premature and simultaneous contraction of auricle and ventricle. The suggestion that the abnormal stimulation may affect auricle and ventricle at the time the normal auricular stimulus is due is supported by such a tracing as Fig. 19. There are two irregular periods, A and B, due to extra-systole. The extra-systole

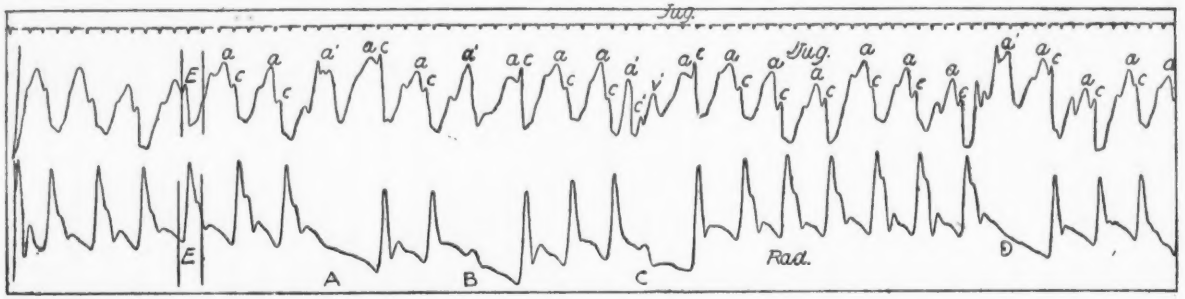

Fig. 17 shows four irregular periods due to extra-systoles, an auricular extra-systole during the irregular period C, a ventricular extra-systole during B and nodal extra-systoles during A and D.

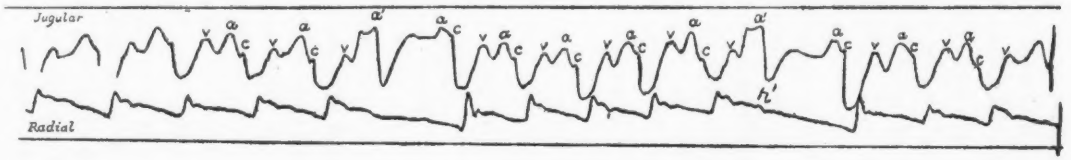

FIG. 18 is from the same patient that gave FIGS. 14 and 17, and shows two irregular periods during which the large broad waves *a'* appear before auricular or ventricular systole was due. They are probably the result of premature and simultaneous contraction of auricle and ventricle—being therefore nodal extra-systoles.

in A is only slightly premature, and the large wave a' appears at the time the normal auricular wave was due. The extra-systole in B appears earlier, with the result that the large wave a' appears before the time the normal auricular systole was due, so that here auricle and ventricle contracted simultaneously and prematurely.

This explanation of the occurrence of the extra-systole arising in the auriculo-ventricular node is not the explanation usually accepted. It has been assumed that these cases are really ventricular extra-systoles, and that the stimulus has passed back and prematurely stimulated the auricle, 'a retrograde auricular extra-systole' as it has been called. But that this explanation is not tenable can be proved on several grounds. As was shown in Figs. 4, 5, 6 and 7, there is no tendency for the stimulation from the ventricular extra-systole to affect the auricular rhythm. If the stimulus does travel back, the rate of backward stimulation must be much greater than the rate at which the normal stimulus travels forward, for as shown in the diagram, in Fig. 16, the time of the ventricular systole is exactly at the same time as the auricular. That this time should be shorter is very unlikely for two reasons—(1) the

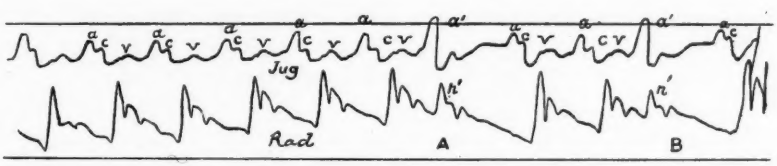

FIG. 19 shows two nodal extra-systoles, a' and r', occurring prematurely and synchronously in the irregular period B.

auriculo-ventricular bundle would be stimulated by the ventricular extra-systole so soon after its conductivity had been exercised that it would not have recovered, and a backward stimulus would therefore be delayed, just as the normal stimulus was delayed after the extra-systole in Fig. 3. (2) The simultaneous and premature contraction occurs in patients in whom the conductivity of the auriculo-ventricular bundle is impaired, as I shall show presently.

In experiment it has been found impossible to induce a backward stimulation of the auricle from a single ventricular extra-systole. I put this matter to Professor Cushny, and I found that he did not believe in the retrograde extra-systole, and in experiment he told me, a premature contraction of the auricle can be obtained only after two or more successive ventricular extra-systoles. On looking up experiments by Hering, who claims to have produced retrograde extra-systoles, I found all his instances to correspond with Cushny's description—that is, the auricle contracted prematurely only after two or more extra-systoles had been excited.

The condition of the a–v bundle in cases showing extra-systoles. From what I have said there are three forms of extra-systole, all arising

demonstrably from different places in the heart. Moreover certain individuals exhibit all these forms, and it is therefore reasonable to infer that all these are due to some common cause. When all the possibilities are considered, the suggestion that the primitive tissue is the seat is the most feasible, the question then arises, is there any further evidence to be elicited as to the condition of this primitive tissue?

The only clinical evidence of the condition of the primitive tissue is to be found in measuring the rate at which the stimulus for contraction passes along the *a–v* bundle from auricle to ventricle. This rate is found by measuring in jugular tracings the time between the beginning of the auricular wave to the beginning of the carotid wave—the *a–c* interval as I have called it. This interval is occupied by three events: (1) the systole of the auricle, (2) the transmission of the stimulus from auricle to ventricle, (3) a minute portion of time taken up by the interval during which the ventricular pressure is rising before the opening of the aortic valves. As 1 and 3 are practically constant, any variation in the duration of the *a–c* interval can be attributed to a variation in the rate of the stimulus conduction in the *a–v* bundle. In normal individuals

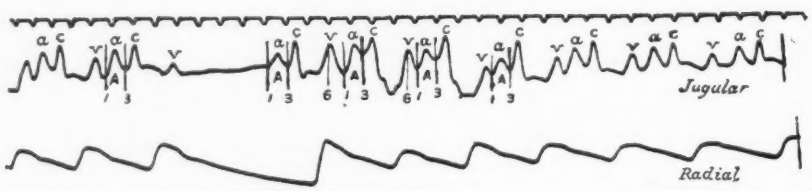

FIG. 20. To show the constancy of the *a–c* interval (spaces A) after long and short periods of rest.

this period very rarely exceeds one-fifth of a second. In hearts acting too frequently, this interval is usually less, sometimes one-tenth. One may suspect something wrong with the *a–v* bundle when this period is one-fifth of a second when the heart is beating rapidly, for the stimulus that quickens the heart-rate will also quicken the rate of conduction when the *a–v* bundle is intact. In healthy slow-acting hearts, in which there is a variation in the heart's rate, it is found that whether the heart's pauses are short or long the *a–c* interval preserves a remarkable constancy. The best instance of this is found in the young, and in those healthy adults in whom there is present that form of irregularity that I have called 'youthful'. Thus in Fig. 20 the long pause is due to a standstill of the whole heart, and is a very typical example of 'sinus irregularity', probably of vagal origin, and here the constancy of the *a–c* interval (spaces A) is very well seen.

On the other hand, if we look at the interval between the auricular extrasystole *a'* and the following carotid wave *c'* in Figs. 13 and 14 we find it markedly increased. This implies that the conductivity in the *a–v* bundle had not recovered from its previous stimulation, and the slowness of recovery is the

proof of inefficiency. In cases of ventricular extra-systole as in Figs. 4, 5 and 6, and in cases of extra-systole arising at the *a–v* node, as in Fig. 16, we find frequently a distinct shortening of the *a–c* interval after a long period of rest, and a lengthening when the period of rest is short. This is well illustrated in Fig. 21, when after the long pause the *a–c* interval becomes less than one-fifth of a second (A_1), but with each succeeding beat it gradually lengthens (A_2 A_3 A_4) until it exceeds one-fifth of a second in duration. In elderly people in whom extra-systoles occur, this variation in the conductivity of the *a–v* bundle is almost always present.

The dropping out of the beat after the extra-systole. In most instances there is a long pause after the extra-systole—the so-called compensatory pause. The reason given by Engelmann, and usually accepted, is that the ventricle is so exhausted after the preceding contraction that it is refractory to the following normal stimulus. While this may be the explanation when the extra-systole is produced experimentally, it does not hold good for the spontaneous extra-systole in man. In Figs. 4 and 5, and in the irregular period B of Fig. 6, there is no compensatory pause, because, as can be seen from the intercalated diagrams in Figs. 4 and 6, the stimulus from the auricular contraction immediately following the extra-systole did get through and stimulated the ventricle. In each case, however, the stimulus took a much longer time to pass from auricle to ventricle. In Fig. 6 the stimulus failed to get through during the irregular period C, for there is no ventricular response to the auricular contraction after the extra-systole. In these and in many similar instances, it is manifest that the reason the ventricle does not contract in response to the stimulus from the auricle after an extra-systole is that the stimulus is blocked in its passage over the *a–v* bundle. Hewlett has recently recorded a case in which the ventricle did not respond to the stimulus from an auricular extra-systole, and the same explanation is given by him. From the foregoing considerations, I make the suggestion that the compensatory pause is not due to the ventricle being refractory, but to the *a–v* bundle being refractory and not conveying the stimulus to the ventricle, which therefore stands still till the next physiological stimulus comes down from the auricle.

The bearing of the condition of the conductivity of the a–v fibres on the question of origin of the extra-systole. There are many interesting facts revealed by this study of the conductivity, and I employ some of them on which to base an argument that demonstrates the origin of the ventricular extra-systole. In Fig. 22 the *a–c* interval A equals $\frac{2}{10}$ of a second while A′ equals about half that time. The point to be elucidated here is, why is A′ so much shortened? If the *a–v* fibres had responded to the stimulus from *a′* there would not have been a longer rest for these fibres, and the space A′ would have had the same length as the other *a–c* intervals. If, however, these fibres were stimulated in the production of the extra-systole (*c′* and ×), then they would be refractory to the stimulus from the auricle (*a′*), and would remain quiescent till the physiological stimulus arrived from the next auricular systole. In this

manner they would have had a longer rest, their conductivity would have been more completely restored, the stimulus would be conveyed across to the ventricle at a greater pace, and a shortening of the *a–c* interval would result, which shortening we find in A′.

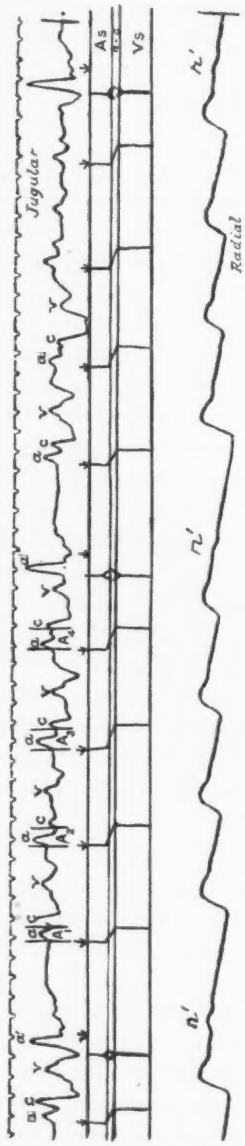

FIG. 21 shows a gradual lengthening of the *a–c* interval (spaces A_1 A_2 A_3 A_4) after the long pauses. The extra-systoles are of nodal origin.

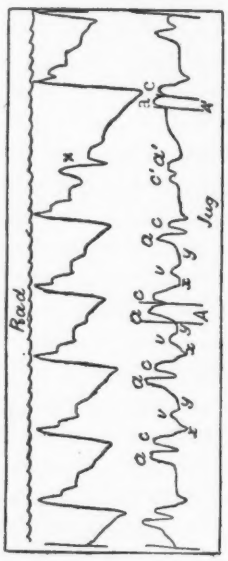

FIG. 22 shows a ventricular extra-systole and a shortened *a–c* interval (A′) after the long pause.

The next question is, did the stimulation of these fibres precede or follow the ventricular extra-systole? I am of opinion that they preceded, and therefore caused, the ventricular extra-systole, because, first, the shortening of A′

implies that the stimulation of *a–v* fibres must have taken place at a time considerably in advance of *a'*; and secondly, if these fibres had been stimulated by a backward wave from the ventricle, the stimulus would have passed back to the auricle and interfered with the auricular rhythm. We see, however, that the auricular rhythm is undisturbed. But from such a line of reasoning it is a justifiable conclusion to infer that the origin of the extra-systole in this case was in the fibres joining auricle and ventricle.

Reasons for attributing the origin of extra-systoles to affection of the remains of the primitive cardiac tube. (1) An *a priori* reason, in the fact that the primitive tube possesses a greater excitability than the auricular and ventricular tissue, and that therefore an abnormal stimulus is more likely to arise in this tissue.

(2) It satisfactorily accounts for the three forms of extra-systole, especially when in any individual two or more forms arise. It seems more reasonable to assume that the one organ or tissue being degenerated gives rise to an extra stimulus, now at the auricular portion, now at the ventricular portion of the bundle and now at the *a–v* node, than to say it arises now in the auricle and now at the ventricle and again at some other part of the ventricle which propagates a stimulus back to the auricle. No experiment has demonstrated a simultaneous and premature contraction of auricle and ventricle, the reason being that no one has stimulated the *a–v* node.

(3) The frequent association of extra-systole with impaired conductivity of the *a–v* bundle implies an affection of the tissue in question. It may be objected that an extra-systole is an evidence of exalted function, while impaired conductivity is an evidence of depressed function. Gaskell has shown that the rate at which a stimulus passes across a bridge of heart muscle can be retarded by narrowing the bridge over which the stimulus for contraction has to pass. In the cases of associated depressed conductivity and extra-systole, there is destruction of some part of the bundle, while the degenerative process which does this renders the part more irritable.

(4) These degenerative processes are more common in advanced years, hence it is in the elderly we find extra-systole most frequent. So far as Dr. Keith has examined the hearts of patients who showed extra-systoles during life, he has invariably found evidence of degeneration of the *a–v* node and bundle. As, however, there was always present degeneration of the coronary artery and muscular fibres of the ventricle, it does not exclude the possibility of ventricular degeneration giving rise to the extra-stimulus, except for the *a priori* reason already given.

I give these reasons, not that I consider they are conclusive, but as suggesting a possible explanation. The matter, however, awaits further experimental work before it can be finally settled. The explanation given seems to me to be more satisfactory than the one hitherto adopted.

THE PARATHYROID GLANDS

Part I

THEIR FUNCTION AND RELATION TO THE THYROID GLAND

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With Plates 21–24.

(From the Physiological Laboratory, Guy's Hospital, and the Pathological Laboratory, Charing Cross Hospital.)

PAGE

I. Introduction 150

II. The Embryonic Theory . . 151

III. The Vitally-Essential Theory 154

IV. Author's Views—

1. The Evidence from an Evolutionary Standpoint . . 158

2. The Evidence from the Comparative Histology of the Thyroid Gland . . . 160

PAGE

3. The Evidence from the Comparative Histology of the Parathyroid Gland . . 164

4. The Evidence from the Embryonic and Cystic Adenomata of the Thyroid Gland . 166

V. Summary 168

VI. Conclusions 170

Bibliography 170

Addendum: The Evidence from the naked-eye anatomy of the Thyroid and Parathyroid Glands . . . 171

I. Introduction.

First described by Sandström in 1880 (42) and regarded by him as embryonic rests of thyroid tissue, the parathyroid glands passed almost wholly unnoticed until, in 1891–3, Gley (18, 19), basing his contention on the effects of experimental ablation, claimed for them a vital importance equalled by few if any other viscera. He was followed by many other investigators, all of whom, with few exceptions, supported his views. Among the first to question the essential nature of the parathyroid glands appear to have been Vincent and Jolly (51), who held that it could not be truly said that the bodies were essential to life, but in their reference to the thyroidal nature of the glands rested content with the conclusion that the latter 'appear capable of functionally replacing' the former 'to a certain extent'. In the same year Richardson (39), after weighing the available evidence, admitted that little was known of the function of the parathyroids and goes no further than to say that 'they appear to be connected with the thyroid and perhaps to have some special relation to the nervous system'.

Despite these occasional doubts the majority of those who have worked on the subject since 1892 accept the parathyroids as glands whose function is essential to life, its suppression leading to death in a few days, and Sandström's original belief has received every year decreasing support.

A study of the literature shows the existence of certain possible fallacies, to which reference will be made below, that are so deep-reaching as to throw serious doubt on conclusions based on the attempted operative removal of the glands. A series of experiments on animals was therefore planned with the intention of obtaining data free from these objections, but it was found impossible to avoid them. The series was abandoned and information sought along different lines. The research thus undertaken consisted of two main parts, the one a detailed examination of the glands in man, the other an investigation of the comparative anatomy, gross and minute, of the thyroid and parathyroid glands in a large number of mammals and birds. The general results of this work have appeared as two papers (16, 17), but in neither was the bearing of the facts there established on the nature of the parathyroids discussed, this consideration, as mentioned at the time, being deferred to a third paper wherein the whole question could be treated.

In the following pages this question will be discussed, and it will be submitted that we now possess sufficient information to warrant a definite opinion on the nature of the glands. This conclusion will not accord either with that of Gley or with that of Sandström and, therefore, before examining the facts at our disposal it will be necessary to review these two hypotheses.

II. The Embryonic Theory.

Sandström (42), to whom as has been stated is due the discovery of the parathyroids, regarded them as embryonic rests of thyroid tissue. He stated that they were present in man and in such domestic animals as he had examined—dog, cat, rabbit, ox, horse—but while in these he found but one gland on each side, in man he met with two. In the same year Wölfler (57) noted the occurrence in the thyroid of areas of young tissue without colloid, and in 1881 Baber described undeveloped portions of the thyroid (1).

Although the history of the parathyroids is held to date back no further than 1880, it is interesting to note that Owen nearly twenty years previously (35), in an account of the anatomy of the Indian rhinoceros, described 'a small compact yellow glandular body' which he found 'attached to the thyroid at the point where the veins emerge', and in the following year Virchow (50) described glands on the posterior surface of the thyroid; but neither he nor Owen recognized any peculiarities of their structure.

The importance of Sandström's paper seems not to have been recognized by his contemporaries, for it passed unnoticed for many years. Horsley (24) in 1885 confirmed Baber's account of the occurrence of embryonic tissue in

the thyroid. Rogowitch (40) believed that this tissue could be transformed into adult thyroid tissue and held that during advancing years there was a gradual conversion of the embryonic to the mature structure. The main trend of opinion was in the direction of regarding the parathyroids merely as immature thyroid tissue, and in the next few years this view received the support of Cristiani (9), Greenfield (21), Zielinska (58), Schaper (43), Schmid (44), and others. For the past ten years this position has been weakened, owing in part to the want of corroborative evidence. It is clear that the strength of the embryonic theory must depend on the following conditions :—

1. That parathyroid tissue should possess the histological features of the embryonic thyroid.

2. That parathyroid tissue should undergo conversion into adult thyroid tissue, that types intermediate between parathyroid and thyroid tissue should exist, and that parathyroid tissue should decrease with advancing age.

3. That parathyroid and thyroid tissues should, occasionally at any rate, be continuous with each other without any intervening septum of connective tissue.

(1) *Do the parathyroid and the embryonic thyroid possess the same histological features?* The answer that has hitherto been given to this question is a negative, and those who have examined both structures appear to have no doubt of the differences between the two. Thus Welsh (54) states that 'a striking dissimilarity is apparent'. Verdun (47) appears to have had no difficulty in distinguishing between the two in any of the embryos he examined. Groschuff (22) investigated the parathyroids in a large number of mammalian embryos and succeeded in effecting the distinction between the two issues. These opinions at first sight appear almost sufficient by themselves to render futile further argument on the identity of the parathyroids and thyroid, but though we admit that the parathyroids as found in adult animals are not merely embryonic thyroid tissue, we need not assume as these observers have done that they are therefore functionally different. As will be shown there is an alternative explanation.[1]

[1] Some authors working from the embryological side of the question state that the cells that are to form the parathyroids are early separated from the primitive thyroid cells and remain distinguishable throughout. Prominent among these writers is Verdun, whose treatise on the comparative embryology of the branchial derivatives in the higher vertebrata (47) contains in addition to his own researches a summary of previous work on the subject. Verdun appears to have experienced no difficulty in distinguishing between the cells of the primitive thyroid and those of the primitive parathyroid, but nowhere in his pages can I find any mention of the points of difference on which he relied. On the other hand, expressions occur from time to time which suggest that this early identification cannot be an easy matter. Thus the primitive parathyroid is referred to as 'un nodule épithélial' (pp. 151, 156), into which grow at a later stage connective-tissue and vascular elements; in another place the parathyroids are styled 'des organes purement épithéliaux' (p. 100). Yet the primitive thyroid (p. 142) 'est constitué par un amas épithélial plein', which is permeated by connective tissue and vessels only at a later date. Since the cells of both are described and figured as being polyhedral, it is not obvious how the distinction is made between 'un nodule épithélial'

(2) *Can and does parathyroid tissue undergo conversion to thyroid tissue? Do intermediate forms exist? Does parathyroid tissue decrease with advancing age?* As regards the two first of these questions there is no unanimity of opinion. The prime importance of noting the presence or absence in the parathyroid of changes indicative of conversion to thyroid tissue has been widely recognized. Briefly the conversion implies the re-arrangement of a solid clump of polyhedral cells into a single epithelial layer of cubical cells lining a regularly formed vesicle; further these cells must show the active function of thyroid cells and secrete colloid.

No conclusive proof of this transformation has been recorded, nor has any observer succeeded in tracing all the intermediate grades from parathyroid to thyroid. Many have failed to meet with any alteration in the parathyroid suggestive of an approaching conversion to thyroid tissue. Among these may be noted Moussu (30), Hofmeister (23), Gley and Nicolas (20), Kohn (27), Blumreich and Jacoby (4), Verdun (47), Ver Eecke (48). On the other hand varying degrees of conversion of the normal parathyroid have been noted by Schaper (43) and Schmid (44), and of the parathyroid after thyroidectomy by Verstraeten and Vanderlinden (49), and Vincent and Jolly (51). In attempting to decide between these it must be remembered that a positive result is of considerably more value than a negative. A dozen parathyroids might be examined without any change being found in eleven of them, but this failure would be more than outweighed by the discovery of a partial conversion in the twelfth. On the whole it may be concluded that though many parathyroids present no sign of conversion to the more specialized (thyroid) type there is some evidence that this transformation does occur, but that the whole series of changes has not been described.

constituting a parathyroid and 'un amas épithélial plein' constituting a thyroid. In another place (p. 75) Verdun, speaking of birds, says that 'après l'éclosion les divers organes, que nous venons de passer en revue [thyroid, parathyroid, etc.] achèvent leur différenciation histologique', and this statement appears to contain the implication that before hatching these organs are not differentiated histologically. The difficulty appears again in the statement (p. 174) that 'la période de différenciation histologique peut se prolonger jusqu'à l'âge adulte'. It is not easy to understand how in face of these last two statements it is possible to identify thyroid and parathyroid, when each is no more than a cluster of embryonic cells budding off from the epithelium of the branchial clefts. Verdun appears to have recognized the difficulty as it affected his predecessors, with whom he says 'ces nodules épithéliaux donnaient lieu à diverses confusions', but he does not make it clear that he himself avoided the 'diverses confusions'.

No more satisfactory are Welsh's pronouncements on the subject. He says (54) that 'the structure of the embryonic thyroid tissue has little in common with that of the parathyroid', that 'it is obvious that the majority of the appearances [of the parathyroids] do not correspond with any condition met with in the embryonic thyroid at any stage in its development', and again, that 'when from this period [the appearance of the thymus] the embryonic parathyroid is compared with the embryonic thyroid of the same age, a striking dissimilarity is apparent'. He gives us no help as to what the little in common is, nor what the striking dissimilarity may be. From the context, however, it is not clear that Welsh studied the embryonic thyroid himself, and it is possible he founds his statements on the work of previous investigators.

The question, Does parathyroid tissue decrease with advancing age? is one of such importance that it is surprising it has escaped attention. Rogowitch (40) believed that there was a partial conversion of the embryonic parathyroid to adult thyroid tissue, but extended observations on this point have been wanting.

(3) *Are parathyroid and thyroid tissue found continuous with each other?* Stress is often laid on the distinct isolation of the parathyroid from adjacent thyroid tissue, and this result has been regarded as militating against the single nature of the two bodies. It would seem only probable that if the two types represent the same functional entity they should occasionally at any rate be continuous, and the fact of their being separate is suggestive evidence of their dual nature. Sandström himself emphasizes the existence of a dividing septum, but recently Vincent and Jolly (52) have stated that one of the parathyroids is frequently in direct continuity with the thyroid.

The occurrence of the undeveloped areas in the thyroid as mentioned by Baber (1), Horsley (24), &c., has appeared of but little moment to investigators, whatever their view of the parathyroids. These masses are continuous with the circumjacent thyroid tissue, and are described as 'undeveloped' portions of thyroid tissue. On these grounds alone one would have expected them to bear closely on the subject of the parathyroids and to have accordingly attracted attention. To find that they bore no relation to the parathyroids would be seriously to weaken the embryonic theory. On the other hand, if the cells of these areas are not different to parathyroid cells the identity of the thyroid and parathyroid is beyond question.

The conclusion must be that while some observations suggest that the parathyroid can develop into thyroid, the contention that parathyroid is merely embryonic thyroid is not proved.

III. The Vitally-Essential Theory.

This theory is founded on the alleged effects of removal of the parathyroids, and it is to these operations, therefore, that attention must be turned. The literature on thyroidectomy, parathyroidectomy, and thyro-parathyroidectomy is too extensive for detailed reference in this paper, and only the more important contributions will be quoted.

The outstanding feature of the operations is the contradictory results obtained. In some the mortality has been very heavy, in others less heavy, light, or even trivial. Thus Gley (19) removed the thyroids and parathyroids from over 50 rabbits and more than three-quarters of these succumbed, while Moussu (30) operating on 19 rabbits lost only 4, and Blumreich and Jacoby (4) found that there was no difference between the effects of thyroidectomy and parathyroidectomy. Cadéac and Guinard (7), Verstraeten and Vanderlinden (49), Edmunds (15), and others all found that the loss of the parathyroids was fatal. Rouxeau (41) performed thyroidectomy on 57 rabbits and only one showed

characteristic symptoms, and Munk (31) stated that 50 % of his monkeys and rabbits, and 25 % of his dogs and cats were not affected by the operation. Vassale and Generali (45) turned their attention more especially to the parathyroid glands, removing these (i.e. to the number of four) and leaving the thyroid. This operation in their hands led to a heavy mortality—9 out of 10 cats and 9 out of 9 dogs dying within a fortnight. Vincent and Jolly (51, 52) performed a series of parathyroidectomies in cats and only 33 % proved fatal; and in a series of thyro-parathyroidectomies on cats, dogs, foxes, monkeys, rats, and guinea-pigs more than 51 % survived the operation for prolonged periods.

Edmunds (15), who has given more attention to the subject than any other observer in this country, gives results which illustrate the contradictory nature of the operative effects. In the case of rabbits he gives the following results (10, 11):—From 7 he removed thyroid and parathyroids; 5 died within 8 days, but 2 survived for many months. From 7 he removed the thyroid alone; 5 died in 6 months, and 2 survived for many months. From 7 he removed the parathyroids alone; 3 died at 35, 82, and 156 days respectively, but 4 survived. As regards dogs, he concluded that they lived or died according to whether a parathyroid was left or not, and at a later date he states (13) that the acute symptoms after thyroidectomy are due to removal of the parathyroids. In a fourth series of experiments (14) he removed 4 parathyroids from each of 9 dogs—3 died in a week, 1 on the 28th day, but 5 survived. Of these last, 2 died after subsequent removal of one thyroid lobe, 1 after removal of both lobes, but 2 survived all three operations. After the partial thyroidectomy had been made complete in these last 2 it is curious to note that they suffered from much the same symptoms (tremors, weakness, &c.) as are stated to follow parathyroidectomy. In a last series of experiments (15) Edmunds appears to return to the belief that it is the presence or absence of one or more parathyroids that determines the survival or death of the animal.

Since the evidence of the function of the parathyroids is founded on the results of their removal, it will be conceded that these experiments leave ample room to doubt its importance.

Restricting our attention to those operations on the parathyroids which have led to fatal results, we find in the first place that only a percentage (varying from about 15 % to about 90 %) of the animals experimented on die or even develop symptoms within a reasonable period. These figures are inclusive of every pathological development subsequent to the operation, yet a certain number of these results must be merely coincidental.[2]

[2] Even in the short series of operations performed in connexion with the present research there arose more than one illustration of the danger of coincidence. The thyroid and parathyroids were removed from a young kitten which was placed after recovery with a healthy kitten of the same age as a control. A few weeks later the control died without any obvious cause being discovered post-mortem. Had the unknown condition that produced death in the control attacked instead the subject of the experiment, it would have been impossible to avoid

As regards the difficulties of the operation of parathyroidectomy, I believe an erroneous opinion is likely to be formed by reading the published accounts. Those who have removed the glands appear to have met with but few difficulties worthy of record, and we are led to infer that the operation is simple. Vincent and Jolly (51) formed this preconception, but as a result of their long series of operations expressed the opinion that 'except in very favourable cases . . . the operation is an impossible one'. On this point I am wholly in accord with Vincent and Jolly. Anticipating little or no difficulty, I found in practice that the obstacles of the operation were so great as to be overcome, if at all, only by the exercise of elaborate precautions. The special difficulties of the operation are as follows:—

1. Parathyroid glands often possess no naked-eye characteristic sufficient to ensure identification.

2. They do not possess that constancy of position with which they have been credited.

3. They are not constant in number.

4. They may be associated with lymphatic glands, thymic residues or accessory thyroids.

5. They may be deeply buried in the thyroid.

6. Both in the thyroid and on its surface they may be microscopical in size.

(1) It has been shown (16, 17) that in the majority of cases the parathyroids could not be recognized with certainty post-mortem except by microscopical section. The liability to error must be still greater when the recognition is attempted on the operating table. It is not sufficient to conclude on naked-eye observation that a small glandular body found in connexion with the thyroid is necessarily a parathyroid, still less that none of the glands left behind in the neck is a parathyroid.

(2) The parathyroids in most animals are stated to lie on the external (lateral) surface and the internal (tracheal) surface of each thyroid lobe, and operators have always sought them in these positions. Though parathyroids can often be found in these positions they also occur elsewhere, their distribution being practically co-extensive with that of accessory thyroids, i. e. from the jaw to the thorax (16, 17). In the goat Moussu (30) has found a parathyroid attached to the submaxillary gland.

(3) The exact number of parathyroids in any animal has always been a source of difficulty. As already mentioned, Sandström (42) believed that, although there were four parathyroids in man, animals possessed but two, and for fourteen years this statement passed uncorrected. Of all the parathy-

ascribing the death to the operation. A still more striking coincidence arose a little later. A full-grown tom-cat had been under observation in captivity for three weeks preparatory to removal of its parathyroids. The operation was arranged for a certain day, but in the morning other matters detained me and the operation was postponed for twenty-four hours. When the morning came the cat was found dead in its cage.

roidectomies done before 1895 it cannot be asserted that any was a complete operation, and their results are consequently open to question. In the latter year Kohn (27) stated that there were four parathyroids all told, except in a few animals (e.g. the rat) which had but two, and from that time to the present operators have been satisfied that a complete parathyroidectomy has been done, provided that four glands have been removed. In the papers already quoted (16, 17) this estimate has been shown to be not correct in man or in other mammals. Parathyroids which possess no characteristic feature raise no suspicion of their nature if they are any distance remote from their commonly recognized position, but if a systematic examination of *every* gland in the neck is made, parathyroids will often be found to a greater number than four, though the actual number varies. Thus among mammals, three examples of the Green Monkey (*Cercopithecus callitrichus*) possessed 1, 8, and 1 respectively; a Collared Fruit-bat (*Cynonycteris collaris*) had 10; a Fossa (*Cryptoprocta ferox*) 6, and three specimens of the Two-spotted Paradoxure (*Nandinia binotata*) 4, 0 and 6 respectively.

(4) The occurrence of parathyroid tissue attached to an accessory thyroid has been noted more than once, but the association of parathyroid with lymphatic or thymic tissue appears to have escaped observation, yet these combinations are not rare in either man or animals.

(5) As is well known, a thyroid gland will not infrequently contain a parathyroid buried deeply in the lobe, and as a rule the nodule thus enveloped escapes attention, but even if some encapsuled structure be noticed it is not possible to distinguish macroscopically between parathyroid, thymic, and lymphatic tissues (all of which occur under these circumstances), or even thyroid tissue itself, areas of which are often encapsuled and contain no obvious vesicles or colloid.

(6) Another source of confusion is the microscopic size of many parathyroids. Isolated clusters of this tissue may be found on the capsule of the thyroid when the whole gland is cut serially. Such parathyroid structures cannot of course be removed in the operation of parathyroidectomy, and the omission will not be recognized unless the thyroid is subsequently cut into serial sections.

Each of these points concerning the parathyroids bears directly on the operation of parathyroidectomy and it can hardly be regarded as easy to perform. On the contrary, no operation can be claimed as complete until a laborious examination by means of serial microscopic sections of all the glands—submaxillary, thyroid, lymphatic, thymus—from the jaw to the thorax has proved the tissue to be absent. Unfortunately, as far as one can find, this precaution has never been taken.

Even if it be granted that in some operations nothing but parathyroid tissue has been removed and in thyroidectomies nothing but thyroid tissue, the results are still open to question. Parathyroids are often embedded in the surface of the thyroid, and, as Vincent and Jolly point out, there is but little

difference between the two to the naked eye, and this little difference entirely disappears when on attempting to dig out the small gland the vascular thyroid starts bleeding. These observers suggest that the deaths ascribed to parathyroid insufficiency are perhaps accounted for by 'the injury caused to the thyroid in endeavouring to excavate an almost invisible body from its substance, combined with the accompanying profuse haemorrhage'. The justness of this criticism is apparent when it is recalled how some operators have attempted to cut out the parathyroids by means of curved scissors, while others, recognizing how their attempts would be frustrated by the slightest haemorrhage, employed a cautery to sear away the parathyroids. The crudeness of these methods and the inevitable injury to the thyroid are obvious.

In thyroidectomy an attempt to remove the large enveloping thyroid lobes, leaving the small parathyroids behind, will require even more skill. Either some bleeding thyroid tissue will cling to the parathyroid or the parathyroid itself will be left injured. Its vascular supply must be interfered with, for parathyroids sunk in the surface of the thyroid are not provided with special vessels, but receive their supply from those in the adjacent thyroid tissue. Vincent and Jolly appear to have realized their difficulties more clearly than previous observers and to have conducted their research with exceptional care and caution. Their opinion becomes of special value and in their second paper (52) they definitely state that their fatal cases were those in which most damage had been done to thyroid or parathyroid tissues, but when either of these was left with little or no damage the animal appeared to suffer no ill consequences.

In face of these considerations we are not justified in concluding that the parathyroid glands have been proved to possess a function of such vital importance that its suppression leads to rapid death.

IV. Author's Views.

1. *The Evidence from an Evolutionary Standpoint.*

A brief consideration of the parathyroid glands from an evolutionary point of view throws some light on their probable importance. As organic life becomes increasingly complex there arise modifications of function and structure, and such of them as are of permanent benefit persist in higher types. A series of organs of successively increasing age are thus formed and certain differences between the oldest and the most recent will be apparent. (1) So long as their original functions are retained, organs will, with lapse of time, become more and more important to the economy, for the longer the period of their existence the more deeply and widely will they strike root in the organism, and the more numerous will be the younger organs in whose origin they have been concerned and whose development they have influenced. Therefore, the older the organ the more deeply and widely will the effects of its

removal be felt. Conversely, an organ, the removal of which is very severely felt, will not be one of recent production. (2) Another point of difference between organs, according to their philogenetic age, arises in connexion with their anatomical variations. A function when first becoming specialized in any type of organism appears in response to certain new conditions which will be of greater or less importance in different representatives of the type. In one specimen the viscus performing the function will be rudimentary, in another more advanced in development, while in a third it will be lacking. At a later period the structure, though present in all representatives, will be better developed in some than in others: it will have no definite size, its anatomical position will be variable and its form inconstant. At a much later stage the viscus, now one of old standing, will have found a definite position, assumed a definite shape, and the demand on its function being constant, its size will be stereotyped. An organ loses its variability and becomes more constant the longer it has been in existence.

The parathyroid glands in man are widely variable in anatomical position, number, and shape, and one subject may have ten or twenty times the amount of parathyroid tissue possessed by another. In mammals, generally, the parathyroids show no constancy of position, size, or shape, while in birds variability is again marked. These facts, therefore, go to show that the parathyroid glands cannot be of any great age.

Those observers who would endow the parathyroids with a proper function essential to life state that their removal leads to a speedy death delayed at the outside by but a few days, often appearing within a few hours. This termination has been noted, for example, in the rabbit. Comparing the effects of parathyroidectomy in rabbits with removal of other organs from the same animals it will be found that the whole thyroid may be removed and the subject, as a rule, suffers not at all, and certainly remains in good health for many months. The spleen may be excised and no untoward result follow. Many other organs (e.g. the suprarenal capsules, pituitary, pancreas) may be extirpated and the animal will survive for some time. The parathyroids are, therefore, no less important than any of the above-mentioned viscera, and more important than some of them. Further, when it is recalled how minute are the parathyroids, it must be admitted that, bulk for bulk, they are much more important than these other organs.

If it be granted that these glands are essential to life, they cannot be regarded as of recent development, yet, if their origin is to be set back to a remote evolutionary period the difficulty has to be met that few, if any, of the organs in the body show such wide variations.

On evolutionary grounds, therefore, the probability is against the assumption that the glands possess a vitally essential function of their own. An alternative supposition that has been advanced—that they are antidotal to the thyroid—is equally unsatisfactory. Before the parathyroids could have thus arisen the thyroid must have assumed to some degree its supposed harmful action, yet the weight of biological evidence is against the supposition. Members of a species

who develop, or tend to develop, a defect in their power of reacting to their environment (such as a noxious thyroid secretion) are at once placed at a disadvantage which inevitably leads to their extermination. They are essentially diseased animals. Such as survive will be those free from the blemish and, therefore, from the necessity for an antidotal secretion. Again, this functional relation between the two glands would imply a relation of size between them, but the parathyroids bear no constant relation in size to the thyroid.[3]

2. *The Evidence from the Comparative Histology of the Thyroid Gland.*

In the present section it will be shown that in some animals and birds the viscus that possesses the anatomical position, shape, and features of a thyroid gland is composed of tissue, indistinguishable from parathyroid tissue, and that in others it is made up of thyroid and parathyroid tissue in varying proportions. Further, it will be shown that gradations of structure from the typical thyroid to the typical parathyroid exist.

At the outset it is necessary clearly to appreciate the histological points of resemblance and of difference between the thyroid and the parathyroid glands. Briefly, thyroid and parathyroid are alike in the arrangement of their connective tissue, blood-vessels and lymphatics, but differ in their epithelial elements. In both there is an enveloping capsule from the deep surface of which pass trabeculae branching and uniting to divide the interior of the gland into compartments polygonal in section. In both, the blood-vessels run in the support of this stroma, finally breaking up into a mesh of capillaries lapped round each compartment. In both, the lymphatics are found in the trabeculae, and running towards the surface unite to form larger channels. The points of distinction lie in the cells contained in the compartments. Attention will first be given to the thyroid cells.

Structure of the Normal Thyroid Gland. The thyroid gland is made up of a number of closely-packed, more or less spherical, closed vesicles lined by a single layer of cubical epithelial cells, and containing in their interior masses of homogeneous colloid. Slight modifications of this typical structure are not uncommon. The epithelium of some vesicles may be columnar, or isolated columnar cells may project from a lining of cubical cells. The cells may be so short as to merit the description of 'squat cubical'. In birds this variety is often found, though in these a flattened type is more usual. The cells, whatever their shape, show changes according to whether or not their protoplasm is distended with the granular precursors of the secretion. In the former case the cells are larger and more oxyphile than those which are fatigued. Sometimes the free edge of a cell is jagged as though there had been considerable detachment of protoplasm in the process of secretion. These changes, dependent on active secretion, have led Langandorff (28), Bozzi (5), Murray (32), and Hürthle (25) to suppose that there are two varieties of lining cells.

[3] The Addendum (p. 171) should follow this section, but for unavoidable reasons has had to be placed at the end of the article.

Another feature of the thyroid is the occurrence of glandular cells lying outside the walls of the vesicles. These are met with quite commonly. They are found singly or in small groups, or in clumps of some size. Their shape depends on the surrounding pressure, but they are usually polyhedral. That they are not merely embryonic is shown by the active changes that take place in their protoplasm similar to those in the cells lining the vesicles, and by the frequent discovery among the larger groups of granular secretion or of drops of colloid. These cells were found to a limited number in the Green Monkey, Feline Gennett, Hyena, Short-headed Phalanger, Purple-capped Lory, Short-toed Eagle and Condor Vulture. Clusters, large and small, were found in Campbell's Monkey, the African Civet Cat, Kinkajou, Dormouse, Guillemot, White Ibis, &c., while the Green Monkey (second specimen) (Fig. 5), Pig-tailed Monkey, Two-spotted Paradoxure (Fig. 2), Barbary Wild Sheep (Fig. 3), and American Jabiru showed fairly large masses of these cells. Of the human thyroid they likewise form a normal constituent, though in my experience they do not tend to form large clusters. They are commonest in the thyroids of infancy, and are found more rarely with increasing years. This last fact accords with Berry's observation that they are more abundant in the young than in the old (2).

It is sometimes noticeable that the larger areas of polyhedral cells show a partial re-arrangement to form small vesicles which are then filled with colloid. The stages of this transformation can be followed by examining a sufficiently extensive number of specimens. In the beginning a drop of colloid appears in the midst of the massed cells pushing apart those in the immediate neighbourhood. The mutual pressure of the cells, aided by the radially-directed pressure of the colloid, leads to the formation around the colloid-containing space of a regular layer of lining cells, cubical or columnar in outline. Small vesicles thus formed will be separated from each other by a varying number of polyhedral cells which have not entered into the new arrangement. Later, however, the vesicles begin to enlarge, more cells are required to line them and the supply of interstitial cells is drawn on till they are considerably diminished in number or even disappear. The stages in the formation of vesicles were well shown in the thyroids of the Pig-tailed Monkey, Feline Gennett, Cunning Bassaris (Raccoon), Prairie Marmot, and Common Mynah, and it is to be specially noted that where the vesicles were smallest the interstitial cells were most numerous and vice versa.

As will be readily seen, any fairly large area of these interstitial cells containing one or two vesicles and a few scattered drops of colloid will present the features that are commonly ascribed to a parathyroid gland.

Two further points concerning the interstitial cells remain to be noticed. They may be entirely absent. In mammals this is not common, though the condition may be met with in the thyroid of human adults and obtained in the Collared Peccary, one of the Suidae. In birds the cells are rarely present to any great number: the American Jabiru was the only marked exception in the present series. Often it is difficult to find any at all, and in sections of the

thyroids of the Angolan Vulture, Egyptian Kite, Long-eared Owl, Crowned Crane (Fig. 1), Night Heron and Maguiri Stork none was recognized.[4]

The second point is that these interstitial cells may outnumber the epithelial cells lining the vesicles. In such cases they often fill the whole of many contiguous compartments. Adult thyroids, made up to a great extent of these solid masses of polyhedral cells, appear to have escaped notice altogether (unless we include the so-called 'embryonic adenomata' which are recorded from time to time as a pathological condition), and it was therefore a matter of surprise to find many examples of the condition in a series of 77 animals. In a Weasel the thyroid was found to have as many compartments filled with polyhedral cells as with vesicles. In a European Beaver (Fig. 4) less than half the compartments contained the specialized thyroid tissue, the majority being filled with polyhedral cells, while the same comment applies to the thyroid of a White-backed Piping Crow (Fig. 6). A Malayan Paradoxure and a Barn Owl were alike in having thyroids which were solid with these interstitial cells, except in certain regions where the transformation to thyroid vesicles had appeared and was apparently spreading. In a Tinamou this change was just beginning, and the formation of vesicles had got scarcely further than an attempt of the polyhedral cells to arrange themselves in concentric groups. A Collared Fruit-bat, a Two-spotted Paradoxure (first specimen), and a Spotted Ichneumon showed to excess the primitive arrangement of cells. Lastly, a Beatrix Antelope, a Fat-tailed Desert Mouse (Fig. 7), a Californian Quail, and an Elenora Falcon (Fig. 8), each possessed a thyroid gland in which were no vesicles, the whole structure being solid masses of polyhedral cells.

It must be clearly understood that not only were these thyroids not embryonic as regards function, but in most cases they were obtained from animals of full growth. In many of them the cells were active, and granules or drops of colloid lay between the cells, and in some (e.g. the Elenora Falcon), the lymphatics were full of secretion. Though the exact ages of most of these animals is not available the term of their captivity is known. Thus, the Fat-tailed Desert Mouse had been kept for three months and the Quail ten months. The Falcon had lived four years, the Two-spotted Paradoxure (first specimen) eighteen months, and the Owl eleven months, while the Bat had been caged for more than seven years. The presence of extensive areas of massed cells is therefore of normal occurrence, even in adult mammals and birds. With rarest exceptions there was no connective-tissue or other barrier between these cells and the true thyroid tissue. Not only were they in direct contact (except for the usual delicate stroma), but the two forms were mixed in endless variety. On the one hand there might be a single vesicle, a cluster of vesicles or an expanse of vesicles set in a mass of irregular cells; on the other hand the solid compartments, single, in small clumps or in large, might be found buried in the midst of a stretch of vesicular thyroid tissue. As a general rule, the vesicles predominated

[4] Clusters of interstitial cells must be distinguished from the lining cells of vesicles cut tangentially. The figure of the Crowned Crane shows the latter but not the former.

near the cortex, the massed cells beneath, and the more extensive the thyroid formation the more did the vesicles encroach on the medullary parts.

These variations, which are if anything commoner in accessory thyroids than in the thyroid itself, are not, I am convinced, morbid, nor do they represent a pathological arrest of development. They are stages in a normal process which must now be described in detail.

The thyroid gland, early in its history, is made up of a mass of polyhedral cells (47). Later, connective tissue grows into it, dividing the organ into compartments, each filled with epithelial cells. As early as the sixth week, in man, these cells become arranged to form the lining epithelium of small vesicles, and by mutual pressure acquire a more definite and regular outline. This change is made gradually, and with its progress more cells are enlisted as epithelium, the surplus of polyhedral cells is diminished, the vesicles enlarge, and finally, the adult and permanent structure is attained. The principal factor responsible for this development is the appearance among the cells of active functioning powers. This change shows itself first in the protoplasm which ceases to be indifferent to stains, and colours faintly with acid dyes. The oxyphile reaction becomes accentuated, the protoplasm is seen to contain granules which finally pass out from the cells and run together to form small drops of colloid. These aggregations will necessarily be found most often at the point nearest to the greatest number of cells (i.e. in the centre of a mass of cells in preference to a more circumferential position), and these will be pushed apart, forming a lumen bounded by the inmost layer of cells. Beyond, the cells will still be polyhedral and arranged without order, but as the drop enlarges the diameter of the primitive vesicle will increase, more cells will be required to line its epithelial walls, and fewer will be left outside. The arrangement finally reached will vary from place to place in the organ, but such cells as remain without the vesicles will not necessarily be embryonic if this term implies undeveloped function. On the contrary, they generally show as active an appearance as those lining the vesicles. As a rule, the thyroid comes to consist almost exclusively of vesicles, but some cells retain their original arrangement, although they develop the power of active secretion. As has already been mentioned, examples were not rare of the major part of the adult thyroid remaining non-vesicular, although engaged in the elaboration of colloid. Such glands, consisting for the most part of tissue possessing the characters ascribed to the normal parathyroid, and only a limited area (usually the cortical) disclosing thyroid tissue, presented much difficulty of interpretation. Though having the anatomical position, shape, &c., of a thyroid gland, they presented the histological features of a parathyroid. The following eight examples of this variety of thyroid occurred among the 77 animals examined.

(1) Both lobes of the thyroid of a Collared Fruit-bat (more than seven years old), were composed of small vesicles lined by cubical epithelium and filled with colloid, but in some compartments the cells were aggregated in solid clusters as in a parathyroid, and, in parts, the whole appearance was that of a parathyroid.

(2) In a Two-spotted Paradoxure (at least eighteen months old), the thyroid was made up of typical parathyroid structure, but on the surface of the gland a definite conversion to vesicular thyroid tissue had taken place, the follicles being lined with regular cubical epithelium and filled with homogeneous colloid. These vesicles were for the most part only one layer deep, but in places they penetrated farther into the gland.

(3) A Malayan Paradoxure possessed a thyroid containing many ordinary thyroid vesicles, but the greater number of the compartments contained an irregular massing of cells similar to those in a parathyroid. In a few compartments the cells showed an attempt at the formation of vesicles.

(4) The thyroid of an Arabian Gazelle was for the most part non-vesicular, by far the greater number of the compartments being occupied by polyhedral cells. Scattered irregularly, but not very frequently, were compartments lined by regular epithelium set round colloid.

(5) In a baby Four-horned Antelope the thyroid consisted of massed polyhedral cells with faintly granular protoplasm, but in one or two places there was apparent a commencing change into mature thyroid tissue.

(6) A specimen of the European Beaver showed a thyroid with an excess of non-vesicular tissue resembling parathyroid tissue. These cells were of the usual type and in places showed attempted arrangements into vesicles, while drops of colloid occurred frequently between them. The regularly formed thyroidal vesicles were lined by a beautifully regular epithelium and contained colloid (Fig. 4).

(7) The thyroid of a White-backed Piping Crow (at least one year old) was made up of more tissue resembling parathyroid tissue than of true thyroid tissue. In places the former showed obvious attempts at a regular formation around central cavities (Fig. 6).

(8) A Barn Owl (at least one year old) showed in each thyroid gland a superficial region composed of regular vesicles lined by short cubical epithelium, and a central region with very few vesicles, but masses of cells similar in every way to those of a parathyroid.

In none of the above examples was there any unusual barrier, connective tissue or otherwise, between the thyroidal and parathyroidal portions; one merged into the other. In none were the non-vesicular areas distinguishable from parathyroid tissue.

3. *The Evidence from the Comparative Histology of the Parathyroid Glands.*

It will be shown in the present section that the parathyroid glands do, frequently and normally, undergo changes whereby their histological features become indistinguishable from those of thyroid tissue. With a connective tissue framework and an arrangement of blood-vessels and lymphatics similar to those of the thyroid, the parathyroid is made up of compartments filled with solid

masses of polyhedral cells. These may possess none of the histological characters denoting activity, clear non-granular protoplasm with no partiality for stains, acid or basic, no secretion between the cells and no collections of colloid either among the cells or in the lymphatics. This essentially embryonic condition is found not uncommonly in man during the first few months of life, but it may persist later and I have seen it in a child of seven (16). In other mammals it occurs, though in them in the absence of reliable information it is difficult to speak as regards its age limits. Birds very commonly show this inactive state of the gland even after growth has been completed. Thus it was noted in a White-backed Piping Crow which had been in captivity for three years, and in an Oyster-catcher after seven years of captivity.

Much more often, however, the cells show the features of activity. They become markedly eosinophile and their protoplasm is seen to be filled with granules. Under $\frac{1}{12}$ in. objective minute collections of granular material may be found lying in the intercellular spaces and not uncommonly the secretion is plentiful enough to form drops. These were found in a Green Monkey, a Kinkajou (Fig. 9), a Fossa (Fig. 10), a Pale-headed Parakeet, an Angolan Vulture and others, including many human subjects. In the Fossa five out of its six parathyroids were in a state of vigorous activity, three of them contained a considerable amount of colloid, and two were occupied by large masses of secretion.

When the parathyroid once assumes secretory powers its cells, exposed now for the first time to the physical effect of collections of secreted material, may be compelled to modify their arrangements, and the remarks that were made above concerning the thyroid and the mechanical effects of its internal secretion on its primitively grouped cells are equally applicable here. The colloid secretion of the parathyroid appears to have the same physical and microchemical properties as the colloid secretion of the thyroid (16).[5]

The parathyroids examined in the course of the present work offered examples of every stage between the solid mass of parathyroid cells and the perfectly formed vesicle. A parathyroid of a White-collared Mangabey contained cells whose arrangement raised just a suspicion of a coming acinar grouping. An African Civet Cat showed an undoubted tendency in the same direction. A Feline Gennett possessed a parathyroid with one or two perfect vesicles filled with colloid. In none of these was there any doubt of the gland being what is commonly recognized as a parathyroid. When however the progress of the parathyroid towards acinar formation has advanced, a stage

[5] No attempt was made in this research to ascertain the physiological action of extracts of parathyroid glands when injected into the circulation because of (*a*) the difficulty of identifying a parathyroid macroscopically, (*b*) the possible vitiation of results by the simultaneous injection of extracts of other tissues, (*c*) the impossibility of ascertaining whether the gland used for the injection contained secretion. Vincent and Jolly (*J. Physiol.*, vol. 32, 1905), state that neither thyroid nor parathyroid extract, when injected intravenously, produced any marked effect upon the blood-pressure, and Easterbrook (quoted by Edmunds, *Lancet*, 1901, vol. 1) found parathyroid extract had no effect when injected.

is reached when vesicles become as numerous as clusters of parathyroid cells, and it is then exceedingly difficult to decide whether the section is that of a parathyroid with many vesicles or an accessory thyroid with much unchanged tissue. The following example illustrates the difficulty. In a Four-horned Antelope there was a small gland near the posterior pole of the left lobe of the thyroid gland. It was made up of polyhedral cells identical with those of a parathyroid, except at the surface where the conversion to thyroid tissue was well advanced, the vesicles lying six or eight deep and apparently in process of spreading more deeply into the gland (Fig. 11).

There was nothing in the sections of this body to suggest that it was either a pathological thyroid or a pathological parathyroid. It cannot be looked on as an unique example of two different organs—thyroid and parathyroid—which are normally separate having become commingled within one capsule. The only satisfactory conclusion is that the gland represents an intermediate stage in the transformation of a parathyroid into an accessory thyroid.

This single specimen is a sufficiently direct proof of the real nature of the parathyroid glands, but its evidence may be corroborated by glands found in certain other animals. Near the anterior end of the lateral surface of the left lobe of the thyroid of a Malayan Bear was found a minute body, less yellow in colour than any of the three parathyroids discovered, but paler than the thyroid proper. One end of it was composed of small, regularly-formed thyroid vesicles, the other of normal parathyroid tissue with a few primitive vesicles. Another specimen of similar import was an accessory thyroid gland which was attached to one lobe of the thyroid of a Golden Agouti at least five years old. It showed chiefly a thyroidal structure, but at one end vesicles were absent and the appearance was that of a normal parathyroid.

In these three examples, as in those thyroids with parathyroidal features previously quoted, there was no delimiting zone of connective tissue between the thyroidal and the parathyroidal areas.

Apart from these specimens many instances were found of direct continuity of tissue between a mass of parathyroid tissue and an underlying or surrounding thyroid. Examples of this arrangement were provided by the Black Ape, Green Monkey, Feline Gennett, Malayan Paradoxure, Side-striped Jackal (Fig. 12), Grey Parrot (Fig. 13), West African Love-bird, Long-eared Owl and Oyster-catcher. In the Love-bird the vesicular structure of one thyroid lobe gave place towards the posterior pole to non-vesicular parathyroid tissue, and this again was supplanted at the extreme pole by more vesicular thyroid tissue (Fig. 14).

4. *The Evidence from the Embryonic and Cystic Adenomata of the Thyroid Gland.*

It has already been mentioned that parathyroid glands may occur buried deeply in a thyroid lobe, and this arrangement is found both in man and in other mammals, but is probably of more frequent occurrence in the latter.

A comparison between these bodies and thyroid adenomata provides confirmation of the foregoing sections.

The stages in the conversion of the embryonic thyroid to the adult vesicular structure have already been traced and the modifying influence of active secretion described. Should there be a collection of cells isolated by stout trabeculae they may remain unconverted until later, and there results an encapsuled mass of polyhedral cells either embedded in normal thyroid tissue or lying on or near the thyroid capsule. These nodules are sometimes referred to as embryonic or foetal adenomata (38), and are often small but may be of considerable size, and Berry (2) figures an encapsulated foetal adenoma occupying at least two-thirds of the whole thyroid lobe (loc. cit., Fig. 28, p. 43).

Adenomata belong to one of three types though intermediate forms occur. (1) Some consist of clumps and columns of cells supported by trabeculae, with or without drops of colloid between the cells, but always without vesicles. (2) Others are made up of collections of regular vesicles always small in diameter, and containing colloid, but separated from each other by a large number of interstitial cells. The relative numbers of cells and vesicles vary. In some, vesicle formation may have advanced only to a slight extent, in others the majority of cells are arranged as lining epithelium to vesicles, the interstitial cells being comparatively few, though still in excess of those found in the adult human thyroid. Less frequently the follicular formation is seen to have affected only one part of the nodule, the remaining possessing a structure like a parathyroid, though the two merge into each other. (3) Lastly, these isolated areas are purely thyroidal on section containing vesicles large and small. Often the vesicles become over-distended with colloid, and a cystic condition results. The resemblance to the normal parathyroid shown by the first, and to a less extent by the second type is obvious. These are the types usually referred to as 'embryonic' or 'foetal' adenomata, and the third type as 'simple' or 'cystic' adenomata (8, 36).

The occurrence of these three forms and the existence of intermediate forms linking them together leaves no room to doubt their common nature, and from what has been already stated it seems equally clear that they represent the usual stages in the development of thyroid tissue.[6] When we come to attempt the distinction between the simple types of adenomata and a parathyroid gland embedded in a thyroid lobe, it is clear we have but little to help us, seeing that the generally accepted histological characters of a parathyroid resemble those of some adenomata.

[6] The change of solid encapsuled masses of cells into cystic adenomata has been noted by Berry (2), but he appears not to have considered its connexion with the subject of the parathyroid glands. He believes that 'solid encapsuled adenomata' become transformed into cysts 'by the gradual breaking down and liquefaction of the centre of the adenoma'. The suggestion seems to be that the transformation is pathological, but in most, if not in all cases, it is strictly physiological—except in so far as the changes are delayed—and the collections of colloid arise by a process of secretion.

V. Summary.

The two theories hitherto advanced in explanation of the parathyroid function we owe to Sandström and Gley respectively. The former looked on the glands merely as embryonic rests; but though there is some trustworthy evidence in support of this view, certain points on which proof may fairly be demanded have not been established. Histological differences which are stated to exist between the parathyroid and the embryonic thyroid have not been satisfactorily explained. The conversion of parathyroid into thyroid tissue has never been conclusively proved to be a normal process, while the correlative fact—the decrease of parathyroid tissue with increasing age—has passed practically unnoticed. Further, the belief that thyroid and parathyroid tissues are always divided from each other by a septum of connective tissue is commonly accepted, and the possible bearing on the whole question of the undeveloped areas described as occurring in the thyroid has not been discussed.

Gley and his followers believe that the parathyroids are glands with a proper function which is essential to life, and they base their opinion on the results of experimental removal of the thyroid and parathyroid glands. These operations show, however, that a percentage of animals too considerable to be neglected suffer little or no effect after loss of the parathyroids. Recent detailed examination of the anatomy of the parathyroids and their variations leads to the opinion that parathyroidectomy is an operation associated with considerable difficulty. As a rule the small bodies cannot be recognized with certainty by the naked eye; they occur in positions other than those generally recognized; they may be more numerous than is commonly supposed; they are not infrequently attached to lymphatic glands, thymic residues or accessory thyroids without raising any suspicion of their existence; they may be microscopical in size and, finally, they may be deeply buried in the substance of the thyroid gland. The operation is therefore open to considerable error, and there is reason to believe that many investigators, not realizing these difficulties, have taken insufficient precautions to avoid them. Lastly, there is the definite statement on the part of some that the more severely the thyroid is damaged in the operation of parathyroidectomy the more likely is a fatal result to ensue, and that the converse of this holds good.

As regards the two theories, it must be concluded that though Sandström's view is supported by certain facts, it has not been definitely proved, and that the great bulk of the evidence on which Gley's interpretation rests is open to grave doubt.

The author's views, which are founded on an examination, naked-eye and minute, of the glands in the neck in 58 human subjects, and 77 mammals and birds, are as follows.

1. Suggestive conclusions are obtained by considering the question from an evolutionary standpoint. The importance of the function of an organ depends on the duration of its existence, the vital functions being earliest

developed. Further, the long-established viscera will not be so subject to anatomical variations as those of recent origin. If the parathyroids possess the supreme importance attributed to them their phylogenetic age would be great, and their anatomical features should be constant as other ancient organs. Yet more than any active organ in the body parathyroids are liable to wide variations. The improbability of the contention that the parathyroids are supplemental or antidotal to the thyroid gland is apparent, when it is stated that the size of the parathyroid glands bears no constant relation to that of the thyroid gland.

2. Observations on the gross anatomical features of the parathyroids point to the thyroid as the organ to which they are related. In human beings the former always occur in the same compartment of the deep cervical fascia as the latter, and they are most numerous in or near the thyroid, especially where the shape of the latter is subject to irregularities and elevations. In this situation accessory thyroids are most often found, and the areas of distribution of these and of parathyroids are the same. Not only are the commonest sites of occurrence of both identical but, in addition, parathyroids decrease with age, while accessory thyroids multiply and are found in the narrow limits recently occupied by the parathyroids.

3. Investigations on the comparative histology of the thyroid gland of mammals and birds show that in addition to the epithelial cells lining the vesicles, there is usually a varying number of 'interstitial cells'. These, when arranged in clumps, possess the characters of the parathyroids, but are directly continuous with the surrounding thyroid tissue. They also show all changes towards the formation of adult thyroid tissue. Sometimes the areas of interstitial cells are more extensive than those of vesicles, and this condition may be found in active adult thyroids.

These cells are of the same nature as the vesicular epithelial cells, and are to be regarded as having failed to become arranged as a regular epithelium. They are quite commonly active, as is shown by the presence of oxyphile granules in their protoplasm and of granular secretion and drops of colloid between the cells. It is the collection of this secretion that induces the assumption of a vesicular structure.

4. The parathyroid glands are made up of clumps of polyhedral cells which usually show the changes associated with activity—protoplasm filled with oxyphile granules, granular secretion, or drops of colloid between the cells. The quantity of secretion is often plentiful, and the drops of colloid force apart the surrounding cells which, modelled by mutual pressure, form a regular lining epithelium and a small vesicle results. This change which is the same as occurs in the areas of interstitial cells may advance until the parathyroid contains so many cells arranged around vesicles that it now approximates to normal thyroid structure. Later still this conversion may be completed.

Sometimes, though not often except in birds, the parathyroid in adults is inactive-looking, being without secretion or granular protoplasm. This condition

usually implies that the gland has never functioned, but it might also occur in an exhausted gland.

Many of the animals examined showed parathyroids in an early stage of vesicular formation. In some the change had advanced so far as to render their distinction from accessory thyroid glands impossible.

VI. Conclusions.

The parathyroid glands are not, as Sandström supposed, merely embryonic in nature. In the majority of specimens there are definite signs of cellular activity.

They are portions of the main thyroid gland which have assumed functional activity but have not yet formed vesicles.

Parathyroid tissue may develop into thyroid tissue, and intermediate types occur.

The secretion of parathyroid glands is a colloid material indistinguishable from thyroid colloid.

The parathyroids, therefore, are glands essentially thyroidal in nature, possessing no peculiar function, but engaged in the active secretion of the same substance as the thyroid gland.

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ADDENDUM.

The Evidence from the Naked-eye Anatomy of the Thyroid and Parathyroid Glands.

The gross anatomical features of the parathyroid glands point to the thyroid as the organ to which they bear an intimate relation. In the human subject they occupy the same compartment of the deep cervical fascia as does the thyroid. The compartment is that which is bounded behind by the layer of fascia arising from the deep covering of the sterno-mastoid, and passing across the front of the carotid vessels to spread over the prevertebral muscles. The anterior limiting layer, also arising from the posterior surface of the sterno-mastoid, runs deep to the sterno-thyroid and sterno-hyoid muscles and in front of the thyroid gland and trachea to join a corresponding process from the opposite side.

The majority of the parathyroids lie in the immediate neighbourhood of the thyroid gland, many in direct contact, some sunk in its surface or deeply buried. Their commonest situation is along the posterior border of the thyroid gland near the point of entry of the inferior thyroid artery. In this position the thyroid lobes often present a noteworthy peculiarity. Smooth and regular over most of their surface, they are drawn out at the hilum into prominences, partially or completely severed from the main gland. It is important to recognize that parathyroids are most frequently found in the situation where the thyroid is most apt to detach, wholly or partially, portions of its tissue, and it is further interesting to note that when the thyroid lobe is smooth and regular near the entry of the artery parathyroids may be absent. On seven occasions, in a series of fifty-eight human subjects, no parathyroid was found near the thyroid lobes, and in five of these the thyroid was unusually smooth in outline. These observations suggest a connexion between the occurrence of parathyroids and the degree of irregularity in shape of the thyroid, and that parathyroids are formed when and where the thyroid tends to produce separated portions of its tissue.

It is obvious that the isolation of nodules of thyroid tissue means the production of accessory thyroid glands, and it has been shown (16) that accessory thyroids are approximately doubly numerous around the point of entry of the inferior thyroid artery than in any other situation. That is to say, the majority of accessory thyroids

are found in the same narrowly limited area as are the majority of parathyroids—an area whose longest measurement does not exceed two or three centimetres.

The anatomical limits of distribution of parathyroids and accessory thyroids are the same. The latter occur from the level of the hyoid bone to the interior of the thorax (39), and parathyroids have been found between as wide limits, even occurring in the chest. One such example was met with in the present research lying behind the sternum, and Vassale and Pianca (46) have recorded others. Two additional instances may be cited. A gland (33) found in the thorax proved on section to be in part true thyroidal, but, in addition contained large tracts possessing a structure 'such as is seen in the embryonic state of the thyroid gland'. Dr. Cyril Ogle, who described the specimen, courteously arranged for fresh sections to be cut for my examination. These sections, though chiefly thyroidal in character, contain tissue which possesses the structure of parathyroid tissue. Another example appears to be that recorded by Osborne (34) who described a body found in the thoracic cavity, its centre being fibrous, but the cortical part resembling 'developing thyroid tissue'.

There is one position in which accessory thyroids are known to occur, but in which parathyroids have not been found. The former occasionally give rise to tumours at the root of the tongue, and though Kanthack (26) denied their connexion with the thyro-glossal duct most observers (6, 29, 37, 54, 55) admit the relation. The absence of parathyroids in this situation is explicable on the assumption that parathyroid tissue may develop into vesicular thyroid tissue, for a normal parathyroid is small and would attract attention only when it enlarged as the result of increased activity, but in this event it would tend to assume the characters of an accessory thyroid.

Finally, parathyroids and accessory thyroids are not found with the same frequency at all ages, the former tending to decrease, the latter to increase from birth onwards. This appears to indicate that parathyroids isolated from the thyroid gland at an early period undergo conversion to accessory thyroids. If this deduction be correct glands intermediate in structure between these two types should exist. Such have been found in the present research.

DESCRIPTION OF PLATES.

FIGS. 1–8. Types of Mammalian and Avine Thyroid Glands with an increasing number of interstitial cells and a decreasing number of vesicles. Figs. 7 and 8 have none of the histological features usually ascribed to thyroid tissue but possess those of a parathyroid gland.

FIG. 1. Crowned Crane (*Balearica pavonina*).

FIG. 2. Two-spotted Paradoxure (*Nandinia binotata*).

FIG. 3. Barbary Wild Sheep (*Ovis tragelaphus*).

FIG. 4. European Beaver (*Castor fiber*). The central mass is isolated by connective tissue and has the histological features of a parathyroid, but is identical in structure with the surrounding thyroid gland.

FIG. 5. Green Monkey (*Cercopithecus callitrichus*).

FIG. 6. White-backed Piping Crow (*Gymnorhina leuconota*).

FIG. 7. Fat-tailed Desert Mouse (*Pachyuromis duprasi*).

FIG. 8. Elenora Falcon (*Falco elenorae*).

FIGS. 9 and 10. Parathyroid Glands showing colloid secretion.

FIG. 9. Kinkajou (*Cercoleptes caudivolvulus*). Colloid secretion in superficial lymphatics.

FIG. 10. Fossa (*Cryptoprocta ferox*). A large lymphatic vessel distended with colloid secretion and one or two smaller collections.

FIG. 11. A small isolated body possessing thyroid features in the cortical regions but parathyroid characters beneath. Found near the thyroid gland of a Four-horned Antelope (*Tetraceros quadricornis*).

FIGS. 12–14. Parathyroid and thyroid tissues in direct continuity.

FIG. 12. Side-striped Jackal (*Canis lateralis*).

FIG. 13. Grey Parrot (*Psittacus erithacus*).

FIG. 14. West African Love-bird (*Agapornis pullaria*). A longitudinal section of the whole thyroid gland showing an anterior thyroidal portion, a posterior parathyroidal portion and a re-appearance of vesicular tissue at the extreme posterior pole.

FIG. 15. Parathyroid tissue attached to a lymphatic gland. From a Green Monkey (*Cercopithecus callitrichus*).

FIG. 16. A small gland composed of accessory thyroid tissue, parathyroid tissue and thymic tissue (Human), separated from each other by connective tissue septa, but the whole enclosed in a single capsule.

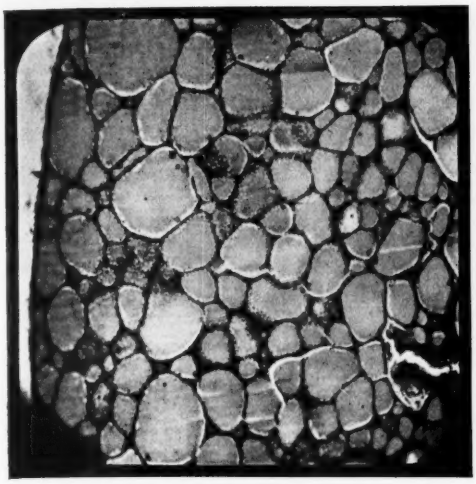

FIG. 1

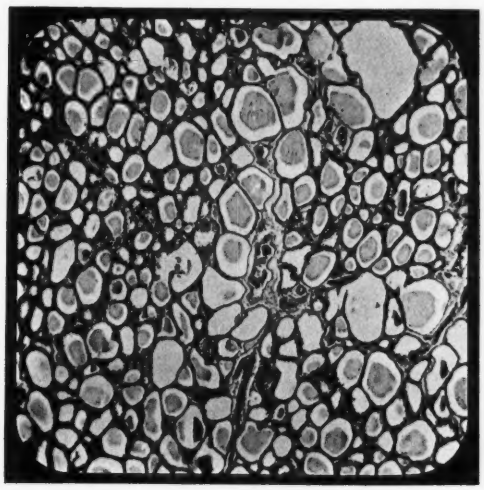

FIG. 2

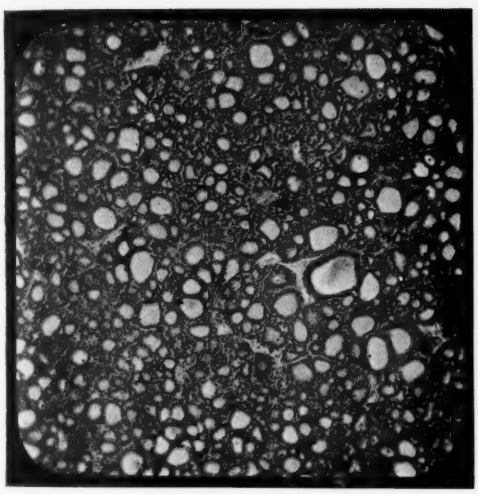

FIG. 3

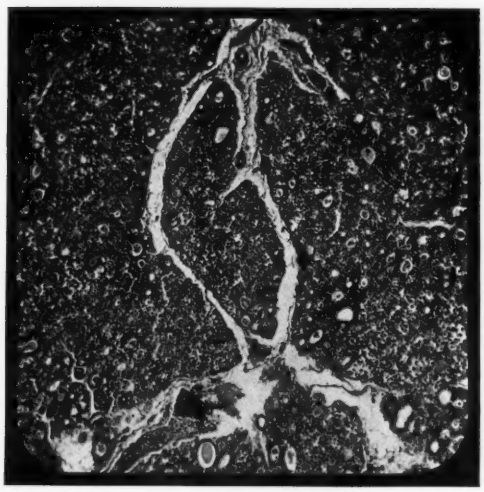

FIG. 4

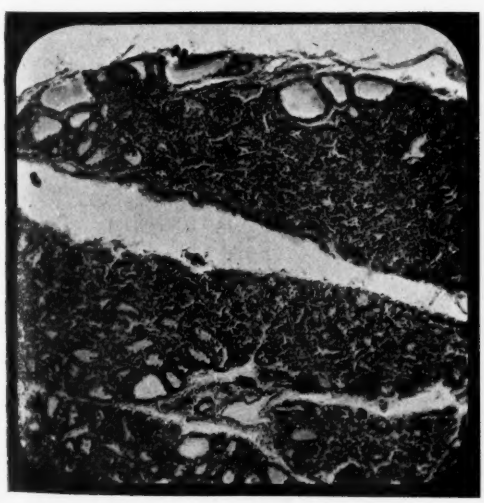

FIG. 5

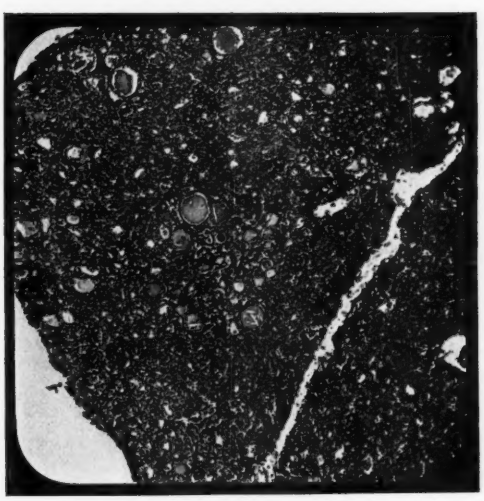

FIG. 6

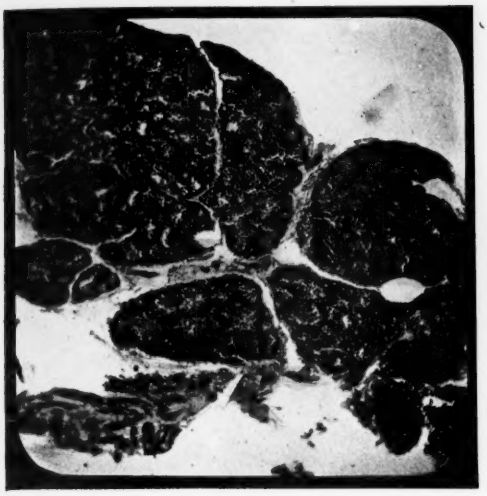

FIG. 7

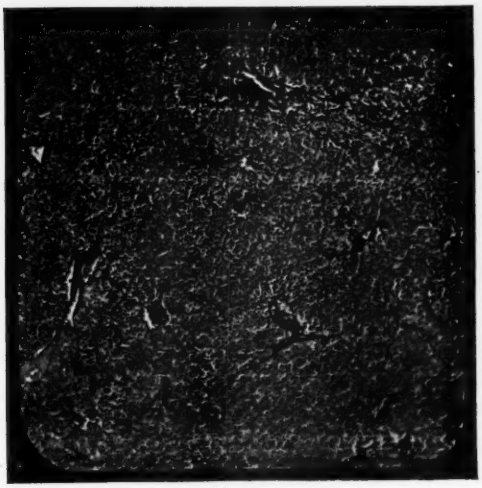

FIG. 8

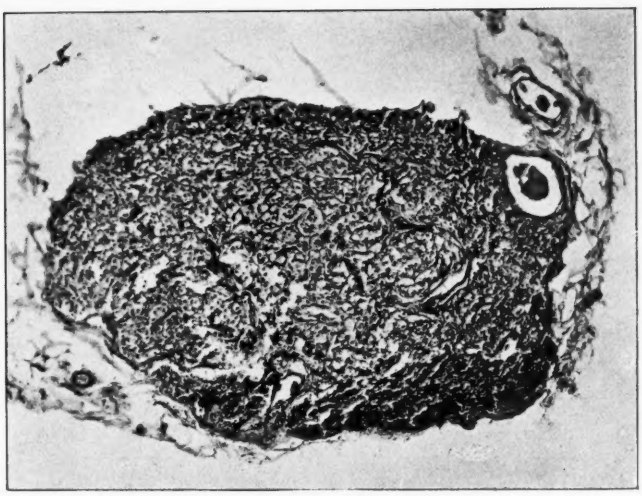

FIG. 9

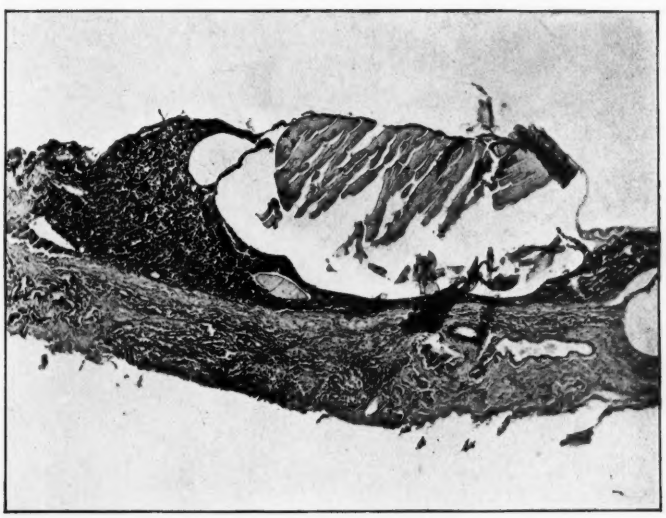

FIG. 10

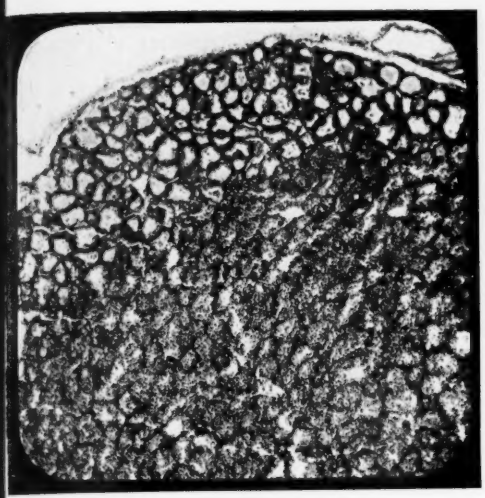

FIG. 11

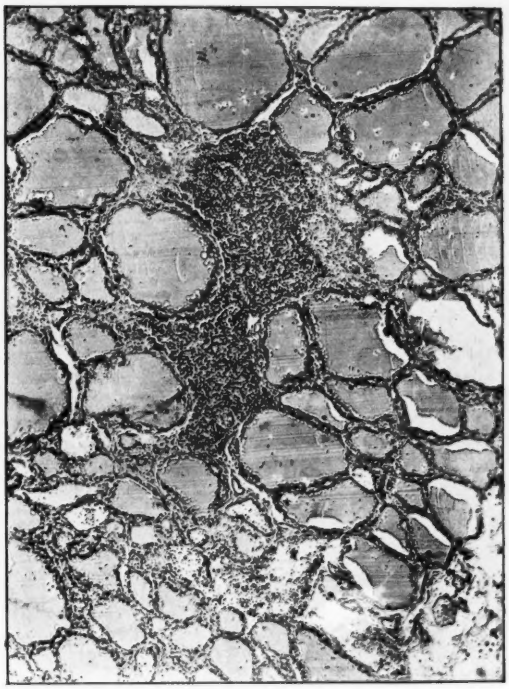

FIG. 12

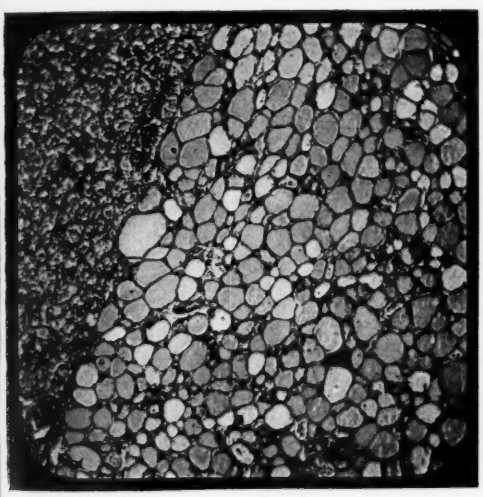

FIG. 13

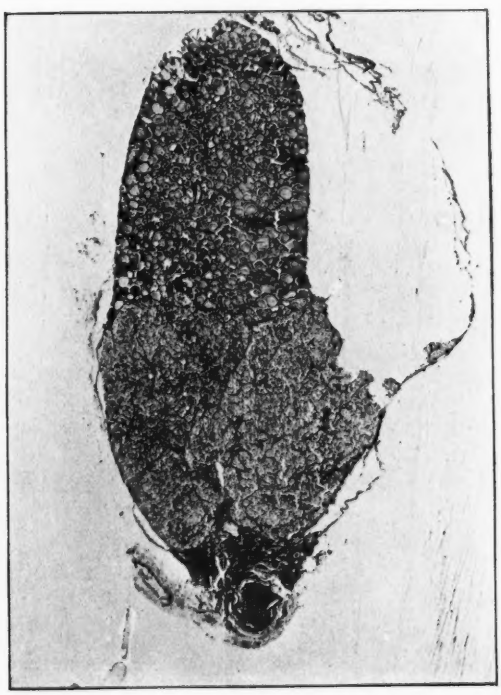

FIG. 14

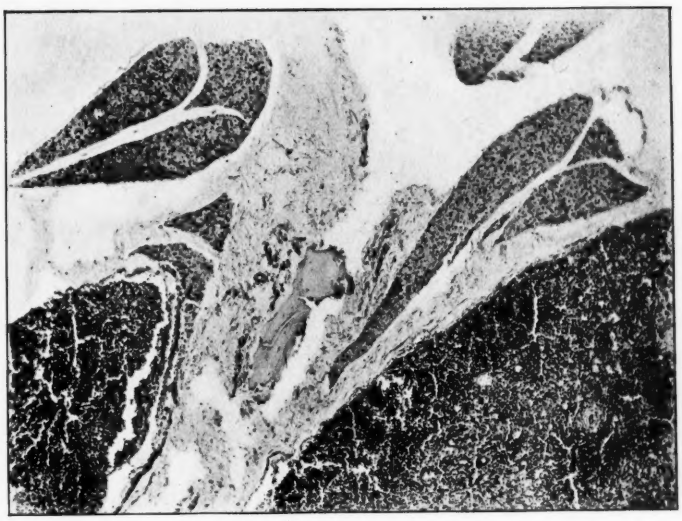

FIG. 15

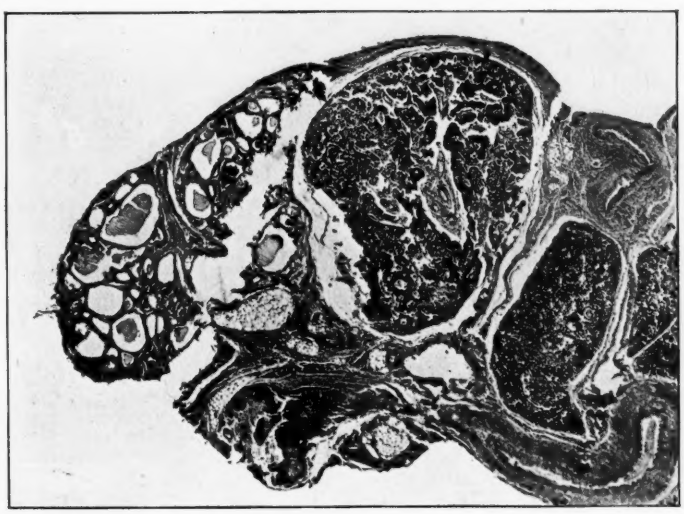

FIG. 16

A CONTRIBUTION TO THE KNOWLEDGE OF THE ACTION OF DIGITALIS ON THE HUMAN HEART

By ALEXANDER G. GIBSON, B.M., M.R.C.P.

§ 1. The following study was made in the Radcliffe Infirmary, Oxford, on a patient under the care of Dr. Mallam, to whom my best thanks are due for the opportunities he has afforded me.

The case was one of a man aged 37, a lately discharged soldier having served in India, who came into the Radcliffe Infirmary on March 17, 1907. On admission he was very dyspnoeic, pale and markedly oedematous up to the groins. The apex beat was not easily localized. The sounds were very feeble and a systolic murmur was detected at the apex. The right side of the chest contained a large quantity of fluid for which he was tapped later, seventy ounces being withdrawn.

On admission he was put on the following mixture:—

Tr. Digitalis (B.P.)	℥ x
Tr. Nuc. Vom.	℥ v
Ammon. Carb.	gr. v
Syr. Scillae	ʒ ss
Aq. Menth. pip. ad	ʒ i

6tis hor.

On March 20, while taking tracings, it was noticed that periods of about one minute occurred in which the pulse was slow, just half the rate that it had been; six days thereafter, on March 26, his pulse was almost continuously slow. The digitalis was stopped on March 29, after which his pulse remained slow for three days; later it had a rhythm, sometimes fast, sometimes slow, the slow rhythm invariably being double that of the fast. *Pulsus alternans* was first noticed on April 6, when the rate was 80. On April 9, since the patient was not improving as he had done on digitalis, he was again given the same mixture as before. On the third day after (April 11), periods of slow pulse were noticed until April 15, when the pulse was continuously slow. On April 15 the dose was lessened to once daily, and from that date till five days after the digitalis was wholly stopped (May 15) there was at first a slow rate with intermissions of a fast rate, later on a fast rate with short intermissions of a slow rate. On May 19 the pulse was noticed to be slow once in the day and the patient was up and walking about.

It may be said that throughout the time this patient was on digitalis, notwithstanding the persistence of the slow pulse, his condition improved and his heart gradually became smaller.

The cause of the slowing of the pulse may with certainty be put down to digitalis, for on withholding it the pulse became continuously fast, on again giving him digitalis it became almost continuously slow.

§ 2. The first point to be decided was the meaning of the slowing of the pulse (Fig. 1). That it was not due to a depression of conductivity was evident from an examination of the time interval between the beginning of the auricular wave on the jugular pulse and the beginning of ventricular systole as shown on the cardiogram. Numbers of measurements that have been made show that this was always about one-fifth of a second. On examining the cardiograms it was seen that in many there appeared to be an extra-systole, suggesting a bigeminal

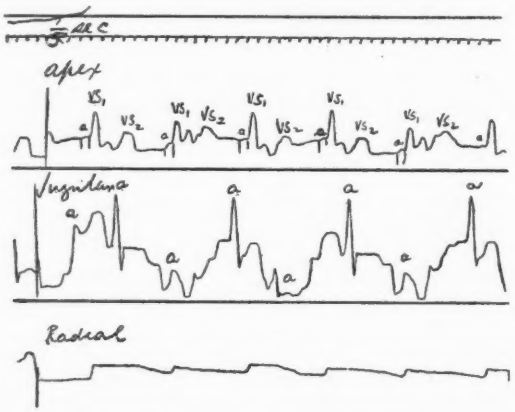

FIG. 1. An example of a record taken during a period when the pulse at the wrist was slow: it shows a time tracing ($\frac{1}{5}$ sec.), the apex beat, the jugular pulse, and the radial. *a* is the auricular beat—well seen in the jugular, but slightly marked also in the apex beat. vs_1 is the first ventricular systole, vs_2 is the second ventricular systole, which is of the nature of an extra-systole (see text).

action of the heart; but in the tracings, taken so as to get a maximum amplitude of oscillation of the tambour, the second wave was many times not sufficiently marked to make the proof of it definite. Never at any time was the second wave seen in the radial pulse. Tracings taken of the carotid showed the same. The X-rays failed to give definite evidence. That, however, we are dealing in this case with one of bigeminal action of the heart is proved by the following observations: The auscultation of the heart during the slow period always gave three audible sounds at the apex. The first was synchronous with the apex beat and was obviously the first sound of the heart; the second sound, sharper in quality and shorter in duration, was to be heard best in the aortic and pulmonary areas; it was the normal second sound: no asynchronism in the action of the two sides was detected. The third sound was constantly present whenever the pulse had the slow rhythm, and no

alteration in intensity with an alteration in the prominence of the second wave at the apex could be detected. At first it was thought that this second apex wave was due to a transmitted beat from the auricle, but careful measurement of the time of commencement of the two shows that the second ventricular beat occurs an appreciable interval *before* the auricular wave in the jugular pulse, and on auscultation in the region of the right auricle it was possible to hear the auricular sound occurring *after* the third sound.

It is to be supposed, then, that the second wave in the ventricular tracing indicates a second ventricular systole not preceded by an auricular beat and not followed by a radial pulse. Presumably there were differences in the strength of the abortive beat, for the wave in the cardiogram, though occasionally

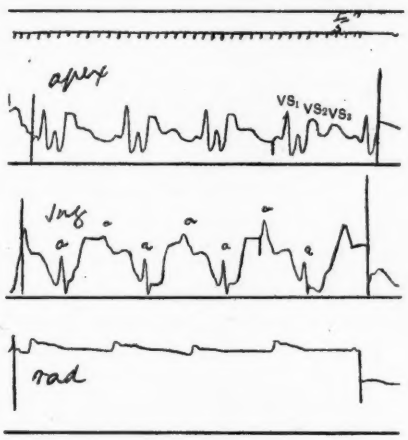

FIG. 2. (Taken on April 17, 1907.) Lettering as in Fig. 1.

large, was frequently nothing more than a slight irregularity on the tracing; yet the third sound at the apex was never found to be absent.

Further proof of this is not wanting. In some tracings, especially those in which the second wave in the cardiogram was large, there was a third rise at the same interval from the second as the second was from the first (Fig. 2). Though no such example was detected on auscultation, a second abortive systole was almost certainly the cause of the third wave, for in one example (Fig. 3) it has so occurred that the second auricular beat, which usually was followed by a normal ventricular systole, was not so followed, because the ventricle having only recently contracted was unable to respond, i.e. the stimulus reached the ventricle in the refractory period.

§ 3. As the result of taking numerous tracings at frequent intervals on this patient, it was possible to obtain records which showed the transition from the quick to the slow pulse and vice versa. Two examples of the former

are given (Figs. 4 and 5). In the first, the fourth and fifth ventricular beats are small; the sixth is large; the seventh, though present at the apex, is only just marked at the wrist; the eighth is large, and at the apex is seen to be

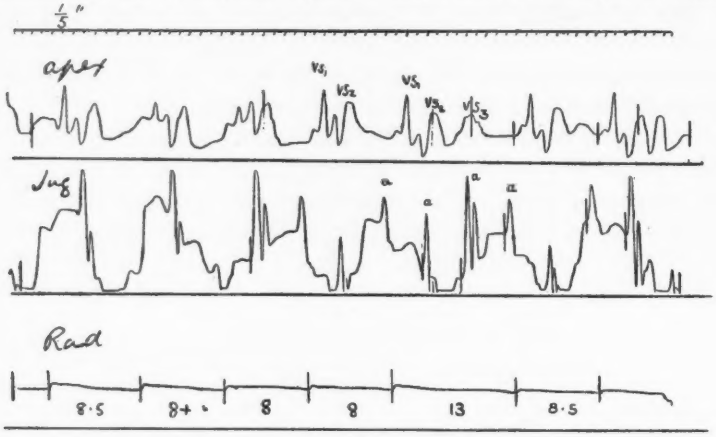

FIG. 3. (April 17, 1907.) vs_3 = third ventricular systole—a second abortive beat; the other lettering as in Fig. 1. The numbers below the radial pulse refer to the intervals in $\frac{1}{5}$ of a second.

followed by an extra beat which is not followed by a radial. The conductivity, as shown by the intervals between the beginning of auricular and ventricular waves, is slightly greater than one-fifth of a second, its normal amount, but shows

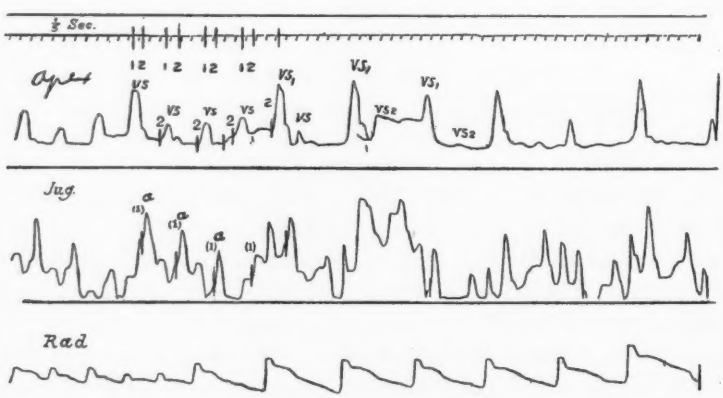

FIG. 4. (May 2, 1907.) The tracing shows the transition in the pulse between the quick and the slow rate. For explanation see text. (Lettering as before.)

no alteration during the transition to the altered rate. The second example has substantially the same features. The fifth ventricular beat is here followed by a small beat at a lessened time-interval; this again is followed by a series of quick beats, only some of which reach the wrist; finally the bigeminal heart

action comes on and with it the slow pulse. The second ventricular beat in the diagram occurs in the last examples after the auricular wave, but it is highly probable that owing to a slight lowering of conductivity as shown by the interval between auricle and ventricle with the quick rate the auricular stimulus has not been the stimulus to contraction, for under the conditions present it could not reach the ventricle. Fig. 6 shows the transition from the slow rate to the fast in the radial pulse. In this and in all the other examples that have been obtained, it is due to the failure of the extra ventricular systoles occurring after each normal systole, so that the normal auricular contraction reaching the ventricle in an excitable period can act as the stimulus.

The mechanism of the slow pulse appears to be as follows: the excitability and rhythmicity of the ventricle increase, an extra small ventricular systole

FIG. 5. (April 26, 1907.) A transition from a quick to a slow pulse. In the apex tracing the ventricular systoles which are followed by a radial pulse are marked as well as those which are obviously extra-systoles, but the irregularity at the period of transition makes it probable that there are more which do not reach the wrist. (The lettering as before.)

occurs before the normal auricular stimulus arrives; the latter reaching the ventricle in the refractory period of the muscle is not followed by a contraction. At the time when the rate changes from slow to quick the excitability and rhythmicity diminishes, the extra ventricular systoles disappear gradually until the auricular systole which previously was not followed by a ventricular systole is capable of exciting the ventricle.

§ 4. *Changes in contractility* cannot be as fully studied as could be desired, but evidence is not wanting to show considerable interference. The frequent occurrence of *pulsus alternans* (Figs. 6 and 7) is evidence of depression of this function. Throughout much of the period when the patient was on the lessened dose of digitalis it was possible to detect, while feeling the pulse at the wrist, a gradual change from a normal pulse to a condition of *pulsus alternans*, and finally a change back to the normal condition: a short

one of these phases is well shown in Fig. 7, which is a pure example of an interference with contractility. As to the condition of contractility during the periods of slow pulse, not much accurate information can be got, but one example showed a *pulsus alternans* with the slow rate (Fig. 8). The quick rate which preceded or succeeded the slow phases sometimes showed *pulsus alternans*, sometimes not (Figs. 4, 5 and 6). The depression of contractility therefore, if present during the slow phase, did not necessarily occur synchronously with the increase in excitability and rhythmicity.

A further example of a depression in this function is shown in Fig. 9, in which before the change from the quick rhythm to the bigeminal rhythm in the ventricle there is a considerable interval in which every other beat only (except in one example) is transmitted to the radial. This observation is apparently the same as was made by Frantzel (1), who found in a case under

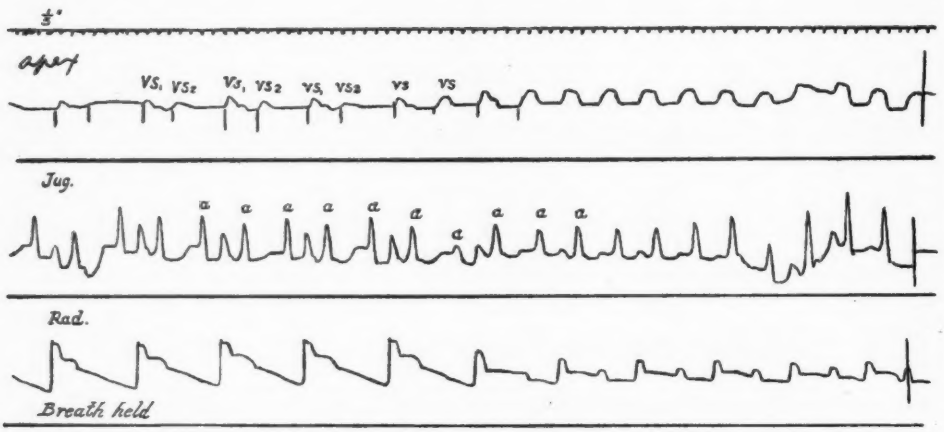

FIG. 6. (May 10, 1907.) Transition from a slow to a quick rate; for the explanation see text.

the influence of digitalis two sets of heart sounds to one pulse wave; no tracings however were taken.

§ 5. *Changes in conductivity* were sought for in the earlier tracings but in vain. It was not until the patient had been taking the smaller dose of digitalis for some time that any change was noticed. Fig. 10 shows a depression of conductivity. Six days after all digitalis had been stopped the *a–v* interval was normal.

§ 6. The study of the action of digitalis on heart muscle, and more especially human heart muscle, in the light of modern views is not very far advanced; it is possible, however, to sum up a few of the effects of this drug on the various functions. On the function of conductivity Mackenzie (2) has shown that digitalis often has a marked depressing effect, causing a delay and sometimes a stoppage in the transmission of the impulse from auricle to ventricle. He states that this effect is by no means invariable, for he quotes one case in which

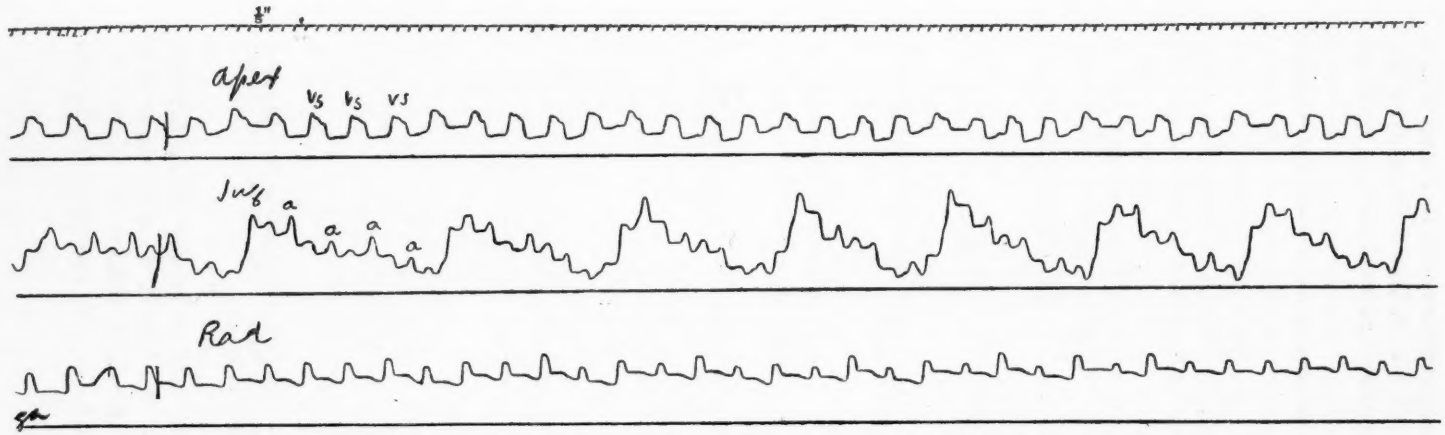

FIG. 7. (May 3, 1907.) The tracing shows a phase of *pulsus alternans*, which begins and ends on the tracing.

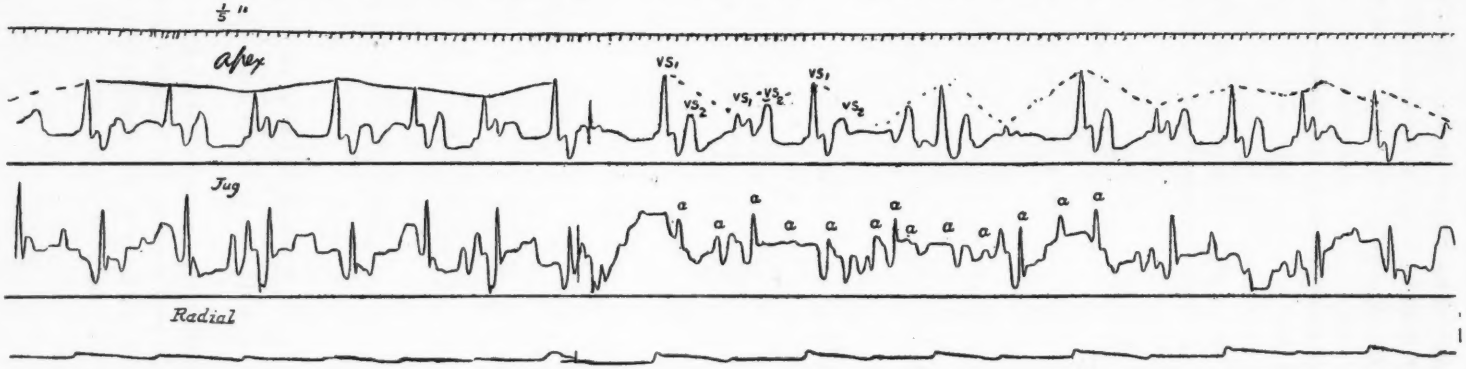

FIG. 8. (April 2, 1907.) The first part of the tracing, taken immediately before the second, shows equal radial beats; the second part shows a condition of *pulsus alternans*.

there was an increase in the conductivity, and mentions that in his experience this function is often not interfered with at all. v. Tabora (3), studying the effects of digitalis on dogs, found a depression of conductivity, which he

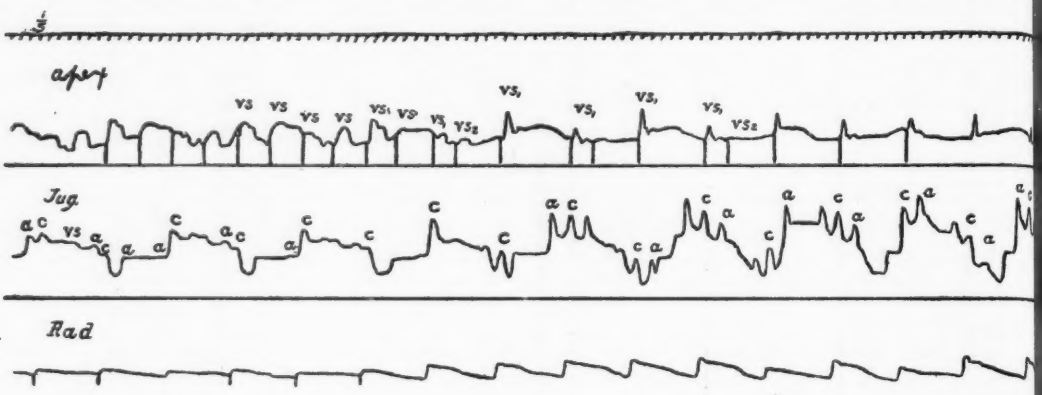

FIG. 9. (May 4, 1907.) Transition from a quick to a slow rate; the first part of the tracing shows double the rate at the apex over that at the wrist.

attributed to the effect partly on the vagus nerve and partly on the muscular junction between auricle and ventricle. The same effect has been described for the isolated frog's heart by Brandenburg (4).

On contractility the action of digitalis is marked. We are not yet in

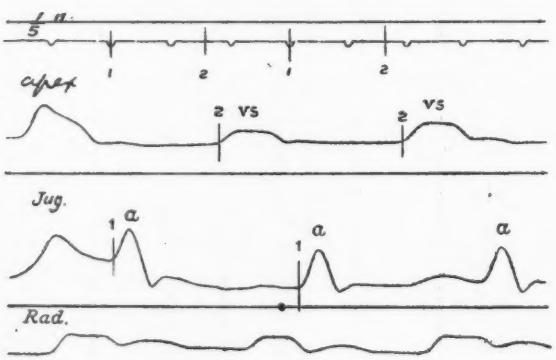

FIG. 10. Tracing taken towards the end of the period when the digitalis was being given (May 5). (The lettering is as before.) It shows the long interval, $\frac{3}{10}$ sec., between the beginning of the auricular and that of the ventricular systole.

possession of a good method for the estimation of an increase of this function. It is possible that the increased force of the beat in the early stages is to be looked upon as an evidence of such. Moreover, Gottlieb and Magnus (5) have shown that the amount of work done at each contraction during the

first stage of its effect in the mammalian heart is two and a half to three and a half times the normal. A depression of contractility is frequently found and well known as one of the effects of digitalis. The *pulsus alternans* so frequently observed has been shown by Wenckebach to be caused by a depression in contractility. In rabbits' hearts failure of a ventricular systole from a pure effect on contractility has been noticed [Pletnew (6)], but so far as my knowledge goes no such observation has been made in man. There is no means as yet for separating in the human heart the effect of digitalis on the two functions of excitability and rhythmicity. This can be done to a certain extent in experimental work by applying stimuli to the heart at varying intervals of time after a systole, when if the excitability is great the refractory period, in which the heart is excitable, will be short.

Brandenburg (4) found that in frogs' hearts which had been poisoned with digitalis there was a depression in excitability. Two forms of pulse in which there is an increase in both excitability and rhythmicity, are common in clinical records, the first is the occurrence of extra-systoles (7), the second is that form of *pulsus bigeminus* and bigeminal heart action discussed by Wenckebach (8); Mackenzie (2) shows that the slowing in the heart's action which occurs with small doses of digitalis is due to a depression of both these functions.

Of the action of digitalis on the function of tonicity we have as yet no knowledge.

§ 7. *Conclusions.* In the case which has been studied we have evidence of the effect of digitalis on four of the primary functions of heart muscle. Conductivity has been diminished but only in the later stages, contractility has been diminished, excitability and rhythmicity have both been increased.

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8. Wenckebach, loc. cit., p. 162.

THE HEART IN A CASE OF STOKES-ADAMS DISEASE

By ALEXANDER G. GIBSON, B.M., M.R.C.P.

(From the Department of Pathology, University of Oxford)

With Plate 25.

§ 1. As the result of a better acquaintance with the anatomy and physiology of the bundle of His, especially the knowledge that a lesion of this bundle produces a slow ventricular rhythm, a number of cases of Stokes-Adams disease have been examined after death to determine the condition of the heart and the state of this bundle. From a search in the literature thirteen cases have been found of which the following is a brief summary: Sendler (1) describes a case in which was found a cartilaginous mural tumour the size of a walnut 1 cm. below the ostium of the pulmonary artery, the valves being intact. Luce (2), in a second case, found a round-celled sarcoma situated in the upper part of the inter-ventricular septum with secondary deposits in relation with two of the sinuses of Valsalva. In Handford's (3) case a large ill-defined thickened mass occupied the upper part of the anterior wall of the right ventricle and invaded the auriculo-ventricular septum. Another tumour occupied the inter-ventricular septum in the region of the pulmonary valves. On section the tumours were found to be gummata. Hay (4) reports a case in which owing to a stretching of the interval between the auricle and ventricle, the bundle was partially obliterated at the point where it perforates the central fibrous body of the heart. No histological details, however, are given. Stengel (5) describes an endocardial lesion which affected a small area at the upper part of the inter-ventricular septum. The important lesion was on the anterior mitral leaflet towards its base and aortic edge. This, a patch of atheroma, extended to the endocardium exactly over the bundle of His where it passes from the auricle to the ventricle. No further histological details are given. A full report is given of a case by Schmoll (6). Underneath the membranous septum was found a widespread area of interstitial tissue causing atrophy of the muscle fibres along the whole course of His's bundle. Underneath the bundle, the same fibrotic process was even more marked, having separated the muscular fibres of His's bundle completely from those of the inter-ventricular septum. The interstitial tissue extended over a space which compared accurately with the course of the bundle. As the bundle was traced towards the ventricle, the interstitial process became less. Microphotographs of the site of the bundle are given. Keith and Flack (7) examined the heart in a case of Grünbaum's and found a gumma of the septum.

A case is reported by Barr (8) in the heart of which Keith found more than half the bundle, at the point where it perforates the central fibrous body, reduced to a fibrous condition. Keith and Miller (9) in another case found a cicatrix in the region of the coronary sinus; part of the inter-ventricular septum formed a cicatricial lamina. The commencement and upper half of the main auriculo-ventricular bundle were completely destroyed. The change was gummatous in nature. The Purkinje fibres in the ventricular extensions of the bundle were normal. A case reported by G. A. Gibson (10) was found to have a considerable increase in fibrous tissue with widespread separation of the muscle fibres constituting the bundle of His; a hard nodule in the liver together with a greatly thickened capsule suggested a syphilitic origin. Aschoff (11) mentions two cases in which he has examined the bundle; in one there was severe sclerosis of the arteries which traverse the knot and the principal part of His's bundle, in the second there was a marked fatty deposit in the same place. A second case reported by Hay (12) had atheroma of the artery which supplies the bundle; and at the point where the bundle perforates the fibrous body of the heart there were patches of recent inflammation which involved the muscular fibres. Jellick, Cooper, and Ophuls (13) described an anaemic necrosis of the region of the bundle consequent upon a recent thrombosis of the arterial supply.[1]

§ 2. The case under consideration was a male aged 59, first under the care of Dr. Freeborn of Clifton Hampden and later under Dr. Turrell of Oxford. Professor Osler, to whom I am indebted for the opportunity of a careful examination of the heart, saw the patient twice and made the diagnosis of Stokes-Adams disease. Tracings taken on both of these occasions showed in the first an auricular rhythm the same as the ventricular, namely, about 80. The later tracings showed an auricular rhythm of 80 and a ventricular rhythm of 35. The patient died of cerebral haemorrhage and the post-mortem examination was made thirty-six hours after death. Putrefaction, though the weather was cold, had advanced considerably.

§ 3. In a detailed examination of the heart it was noticed that putrefactive changes were well marked. The heart was larger than normal, the left and right sides being enlarged in the same proportion. The sub-epicardial fat showed a marked increase; only on two very small areas anteriorly and a rather larger one about a square inch posteriorly, was it possible to see the ventricular muscle. On the exterior of the auricles there was an increase of sub-epicardial fat, though in proportion to their total surface more muscle was visible. The deposit of fat on the conus arteriosus was more abundant than normal.

[1] A case, the details of which I have not had the opportunity of consulting in the original, is published by Vaquez et Esmein, *Bull. et mém. de la Soc. méd. des hôp.*, Paris, 1907, vol. 24. Two further cases are published in abstract in the *Münch. Med. Woch.*, 1907, vol. 54, p. 636, by Fahr; in one the inter-ventricular septum was the site of a tumour which was penetrated by the muscle fibres of the bundle, in the other there was a cicatrix at the place where the bundle divides into right and left halves.

The right auricle was moderately enlarged, but the appendix was small and shrunken, its cavity was smaller than usual. Here and there under the endocardium were pale areas which on section were seen to be fatty deposits. The muscular bands were little if at all thickened. The cavity of the left auricle was enlarged; the appendix was a mere tag on the surface and its cavity was much reduced, this reduction had probably taken place as the result of the incorporation of part of the appendicular cavity into that of the auricle, for, round the appendicular opening was a circular area of muscle about a quarter of an inch broad, suggesting the transverse columns of the auricular appendix in the normal state. The endocardium was thickened, but no area of subendocardial fat was seen. The walls were slightly thicker than normal. The right ventricle was dilated; the muscular bands on the inner surface were flattened. There was an increase in the thickness of the muscle and towards its outer surface extensions of fat from the subepicardial deposit were visible between the muscle fasciculi. A few pale areas of fatty deposit were seen under the endocardium. Nothing could be detected of the right limb of His's bundle, but the thread-like strands connecting the columnae carnae whose significance has been established by Tawara (14) were as numerous as in the normal heart. The muscular tissue as seen through the endocardium and on section was a deep brown, but in the middle of the inter-ventricular septum it was of a much paler colour and appeared more normal. The left ventricle was enlarged and its walls were markedly hypertrophied. One or two minute whitish areas were seen under the endocardium. No trace could be seen of the left limb of His's bundle. The tricuspid valve was normal. The mitral valve was normal except for a few areas of thickening, probably atheromatous, towards the edge of the anterior cusp. The pulmonary valve was normal and the aortic very slightly thickened. A few small areas of atheroma were detected in the aorta; the pulmonary artery was normal. The orifices of the coronary arteries were normal; the walls of both were thickened and here and there were small areas of atheroma; the lumen was not narrowed in either.

§ 4. The portion of the auricular and ventricular septum containing His's bundle was cut out after the whole heart had been fixed in 4% formol; it was then taken through alcohol and chloroform and finally embedded in paraffin in the usual way. A similar portion of a normal heart from a person of a like age was embedded. Serial sections were then cut, as far as possible in the long axis of the bundle, and stained by Van Gieson's method.

In the accompanying figures will be seen drawings of some of these sections, three from the normal and three from the diseased heart showing the relations of His's bundle. The sections of the heart under consideration show the area occupied by the bundle to be increased, though the length of tissue which it has to traverse is somewhat longer by the stretching which has occurred owing to the dilatation of the left ventricle. The size of the central fibrous body of the heart is little if at all larger than normal, yet there is a diffuse increase of fibrous tissue in the neighbourhood stretching as far as and into the ventricular septum.

Under the microscope, the auricular muscle is extensively infiltrated with fat, the muscular bundles being squeezed between the distended fat cells. The same condition in no lessened degree is present where the muscular fibres constituting His's bundle enter the central fibrous body and continues until it reaches the sides of the inter-ventricular septum. Purkinje fibres are present on both sides of the septum after the two limbs of the bundle have spread out—an observation which agrees with one of Keith's in a similar case. A microphotograph of the bundle as it passes through the fibrous body is shown in Fig. 3.

§ 5. The examination of the microscopic features of this heart have been hampered by the extent to which putrefactive changes had gone on before it was fixed. Numbers of bacilli were seen in every field. The muscle fibres could still easily be distinguished, but of their internal structure nothing could be ascertained except that, in the ventricle especially, there was marked brown atrophy. The nuclei and striations could not be thrown into relief by any of a number of stains that were tried. It is not possible, therefore, to pronounce an opinion on the nature of the remaining fibres of the bundle, but so far as their outward shape and their opacity may be taken as a guide, they were not abnormal.

Another feature detected under the microscope and in places obvious even to the naked eye was the presence in the unstained sections of brown pigmented areas in relation with and about the same size as the fat cells. They have been detected chiefly in the neighbourhood of the entry of the bundle into the central fibrous body, but also in the course of the bundle and elsewhere away from the bundle. Many of these areas contained fat as well as pigment, as was shown by staining frozen sections with Nile Blue sulphate A according to Lorrain Smith's method (15). Professor Aschoff who has been kind enough to examine sections for me writes to say that the appearance is produced by the action of formol on blood pigment which has diffused out of the blood vessels as a result of putrefaction; though I have not myself verified the fact, it is borne out by finding much of the pigment in association with the fat surrounding the vessels.

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EXPLANATION OF FIGURES.

FIG. 1. Drawings from three sections, stained by Van Gieson's method, of a normal heart (two and a half times the actual size), to show the relations of His's bundle. *a* = auricular muscle; *b* = ventricular muscle; *c* = mitral valve; *d* = attachment of septal cusp of tricuspid valve; *e* = His's bundle.

FIG. 2. Drawings from three sections of the heart described (thrice the actual size). The lettering is the same as in Fig. 1. Van Gieson's stain.

FIG. 3. Microphotograph of His's bundle as it enters the central fibrous body of the heart, portions of which, stained dark, can be seen on either side. The clearer spaces between the longitudinally-coursing muscle fibres had been occupied by fat.

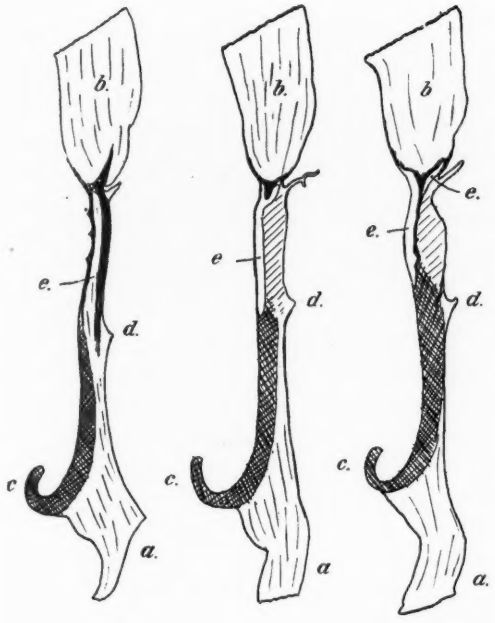

FIG. 1

FIG. 3

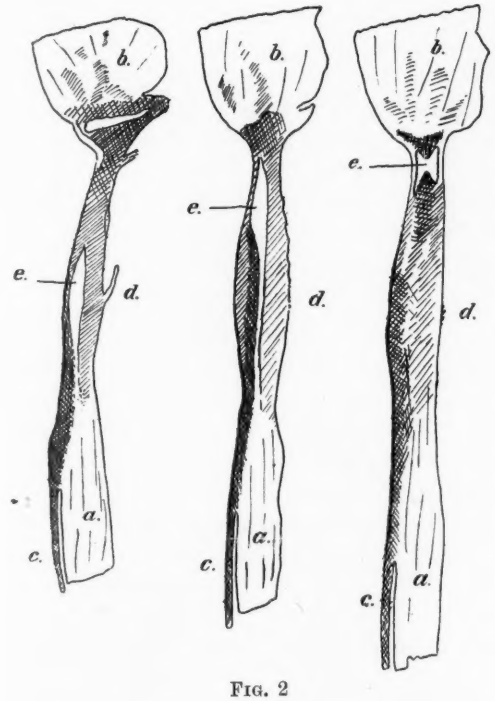

FIG. 2

CERVICAL RIBS AND THEIR RELATION TO ATROPHY OF THE INTRINSIC MUSCLES OF THE HAND

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Medical Officer in charge of the Electrical Department, St. Bartholomew's Hospital.

With Plates 26 and 27.

In the St. Bartholomew's Hospital Reports for 1893, I published a short paper on 'Symmetrical Atrophy affecting the Hands in Young People', and drew attention to a class of case which, so far as I am aware, had not previously been recognized. In that paper six cases were recorded, and these were also shown at a clinical meeting of the Neurological Society at about the same time.

The symptoms of the condition were then described as follows:—

'The ball of the thumb is noticed by the patient to be getting thin, and the movements of the thumb to be weak and awkward. There is a history of pain or tingling in the fingers, in the wrist, or in the arm and forearm; this usually comes on before the atrophy is noticed. The affected muscles become wasted, and some or all of them show a well-marked reaction of degeneration. The changes are not limited to muscles supplied by a single nerve-trunk, but are found both in median and ulnar muscles. Only the intrinsic muscles of the hand are affected. The cases do not go on to progressive muscular atrophy and under treatment some of them have improved.'

Since that date other observers have reported cases belonging to the same class, and in 1902, E. F. Buzzard[1], in a paper on 'Uniradicular Palsies of the Brachial Plexus', assigned the group a well-defined place by showing that the condition should be regarded as due to an affection of the first dorsal nerve-root, and that an anaesthetic area corresponding to that nerve-segment might often be found, if looked for, on the ulnar side of the forearm and hand. No obvious reason for the occurrence of a localized neuritis in such a situation could be given, and the etiology of the condition therefore remained uncertain. It was known, it is true, that cervical ribs occurred, and that they might interfere with the brachial nerve-roots, but they were seldom met with in clinical practice until after the introduction of X-rays, which have shown that they are by no means uncommon. Thus I had under my care at St. Bartholomew's Hospital in 1893 a patient of Mr. Lockwood's with wasting and reaction of degeneration

[1] *Brain*, Lond., 1902, vol. 25, p. 299.

in the intrinsic muscles of the left hand and with a bony prominence on the left side of the neck. This was removed by operation, and its removal was followed by the gradual disappearance of the nervous symptoms. And yet by some strange perversity of thought, and perhaps because in her case the tumour in the neck was easily felt, this patient was considered by myself to belong to a different category, although from what we now know she really furnished the clue to the group of cases of atrophy of the muscles of the hands which was then receiving my interested attention.

Since the year 1893, I have seen a considerable number of examples of wasting of the intrinsic muscles of the hands of the type now under consideration, perhaps in all about twenty-five cases, the great majority of them in female patients, and although I have several times felt a wish to publish my notes of the whole series, I have as often restrained myself from doing so because of a conviction that the time for their publication had not arrived, but that some fresh light upon a somewhat mysterious group of cases might one day appear. This fresh light appears to have been thrown upon the cases by Dr. William Thorburn in a paper read by him in the autumn of 1904, and subsequently printed in the *Medico-Chirurgical Transactions*[2], in which two cases of atrophy of the intrinsic muscles of the hands were shown by skiagrams to be associated with the presence of cervical ribs. He pointed out that the cases presented a great resemblance to certain recorded examples of uniradicular paralysis of the brachial plexus 'whose pathology had never been adequately explained, and in none of which had the possible presence of a cervical rib been specially excluded'. His paper contained the following passage:—

'Although cases of supernumerary cervical ribs are not very rare and are tolerably well recognized, my excuse for bringing the matter before you lies in the fact that I have been unable to find any complete description of the clinical symptoms which they produce, and especially in the slight notice which they have attracted from neurologists. As illustrating the latter fact, we may note that in Duval and Guillain's *Monograph upon the Brachial Plexus*, the seventh cervical rib is not even mentioned, and that several cases of radicular paralysis of the plexus have been recently published, in which this condition, although a probable cause of the symptoms met with, is not considered as an etiological factor.'

In consequence of Dr. Thorburn's paper I commenced to take X-ray photographs of the cervical region of such of my own cases as I could find. Unfortunately, the search for old hospital patients in London is full of disappointments, and I have only been able to trace a few of the whole number of cases of atrophy of the hands which I have seen at different times. Figs. 1 and 2, however, show the cervical regions of two of my early patients, whom I regarded as types of the condition originally described in my paper of 1893.

[2] 'The seventh cervical rib, and its effects upon the brachial plexus'. *Medico-Chirurgical Transactions*, Lond., 1905, vol. 88, p. 109.

Both had bilateral atrophy, but while in one the condition has not changed much in the past twelve years, in the other the muscular disability and wasting has advanced considerably, and this patient cannot now button her clothing without great difficulty. In all other respects these patients are in good health; and the patient whose neck is shown in Fig. 2 is actively engaged as a cook in a large West-end shop. Fig. 3 shows another case with a rib on one side only, and in this case the atrophy and reaction of degeneration are also present on that side only.

The result of the X-ray examinations of such of my old patients as could be traced supports Dr. Thorburn's opinion, that the cervical rib is an important factor in the causation of atrophy of the muscles of the hand, for well-marked cervical ribs were found to exist in ten out of fourteen cases examined. Moreover, a rib was present on both sides in eight persons who presented symptoms on both sides, but only on one side, and that the one affected, in two cases with wasting of one hand only. Several of my patients have volunteered the statement that pressure in the neck over the site of the supernumerary rib produced a tingling sensation, which was felt on the inner side of the forearm and in the fingers.

A possible reason for the tardy discovery of a relationship between cervical ribs and atrophy of the intrinsic muscles of the hands, may be found in the fact that many instances of cervical ribs have been observed in persons who presented no signs of muscular atrophy or any other interference with the cords of the brachial plexus, but it is manifest that the influence exercised by the rib upon the nerve-trunk must be a mechanical one, the rib causing pressure or stretching of the nerve-trunk, and thus one can readily understand that whereas some cervical ribs might interfere with the plexus by reason of their shape or position, others might be so disposed as to lie in a direction which kept them entirely clear of the brachial plexus. Indeed the cases of cervical rib in which a bony prominence can be felt with ease are usually free from any pressure symptoms so far as the brachial plexus is concerned, and the photograph of such a case is given here (Fig. 4) in order to show that the X-ray shadows indicate a straight rib, whereas the other figures show ribs with decided curves. The curved appearance is very pronounced in most of the cases with nerve symptoms, and it helps to explain why some cervical ribs are harmless and others injurious. That a cervical rib may interfere with the cords of the plexus is made clear by the reports of dissectors. In the *Proceedings* of the Anatomical Society of Great Britain and Ireland for May, 1900, there is a detailed account of the dissection of two cases of cervical rib by Dr. Llewellyn Phillips, formerly Demonstrator of Anatomy in St. Bartholomew's Hospital. In the first of the two cases the brachial plexus is stated to have been normally constituted; the lowest cord, formed of the eighth cervical and the first dorsal nerves, crossed over the cervical rib, grooving it. The body of the cervical rib was pointed in front and was connected with the upper end of the manubrium sterni by a fibrous band. In the other case also there were grooves on the upper surface of the cervical ribs

on both sides which were occupied by the brachial plexus, and both the ribs ended in front in a rounded point, from which a fibrous band ran to the sternum. The brachial plexus was normally constituted, as in the first case, and it was the cord formed by the eighth cervical and first dorsal nerves which crossed over the cervical rib and grooved it.

Again, in the *Proceedings* of the same Society for July, 1892, Dr. Addison is reported to have shown a specimen taken from a dissecting-room subject, which presented a cervical rib on each side. The subject was a female, aged 56. The lowest cord of the brachial plexus grooved the upper surface of the supernumerary rib, and a fibrous cord connecting the point of the rib to the sternum was present. No note is made of the condition of the hands in either of these patients, but this might naturally have been overlooked in the absence of any information tending to connect cervical ribs with muscular atrophy.

In one of my cases an operation for the removal of the cervical rib was performed by Mr. Rawling, who has informed me that the rib was much curved forwards, and was bony in its entire length, save for a short cap of cartilage at its anterior extremity. This was quite free, without ligaments or attachments. The rib was broad and flat and somewhat resembled a first dorsal rib, its inner border was very sharp, and it had a groove above for the eighth cervical nerve, which was sharply kinked over the anterior part of the rib. The first dorsal nerve passed under the rib, and was also slightly displaced and pressed on. Both cords were of the usual size, and united together a little beyond the rib.

Since the appearance of Thorburn's paper, a good deal of fresh interest in the subject of cervical ribs has been provoked, and a number of papers have been written on the subject. Among these authors I would specially mention Dr. Hinds Howell, who has communicated a very complete paper on this subject to the *Lancet*[3]. Howell's paper gives notes of sixteen cases, and is further of interest because it contains a camera photograph of a bony specimen in the Museum of the Royal College of Surgeons. This specimen has cervical ribs on both sides, but that on the left side is short and irregular in shape and lies in close relationship to the first true rib. Such a rib, photographed by X-rays in the living subject, would probably give an impression on the plate of an overgrown transverse process of irregular outline, an appearance which is sometimes seen in X-ray photographs of the cervical region. It is worthy of mention, that among my patients two out of the four cases which have been counted as not showing cervical ribs present an irregularity of this kind in the size and shape of their seventh cervical transverse processes; I do not lay stress upon this, however, because abnormalities of one kind or another occur fairly often in this region in normal persons, but an examination of a considerable number of necks by the X-rays shows that, in general, the seventh transverse processes appear decidedly shorter than those of the first dorsal vertebra, and I have

[3] 'A consideration of the symptoms which may be produced by seventh cervical ribs.' *The Lancet*, Lond., 1907, vol. 1, p. 1702.

observed this to be the rule both in persons whose necks are long and slender, and in those whose necks are short and thick.

Finally, in respect of surgical operation for the removal of the cervical rib, it may be said that its complete removal is an operation of some difficulty, and is apt to be accompanied by injury to the brachial plexus with an increase of the paralysis and wasting, and, on the other hand, incomplete removal of the projecting part of the bone only may be followed by a relief to the symptoms which is not complete, inasmuch as I have met with two instances showing a return of pain and muscular weakness after the lapse of some time, with evidence, from the X-rays, of new bone-formation at the free extremity of the resected rib.

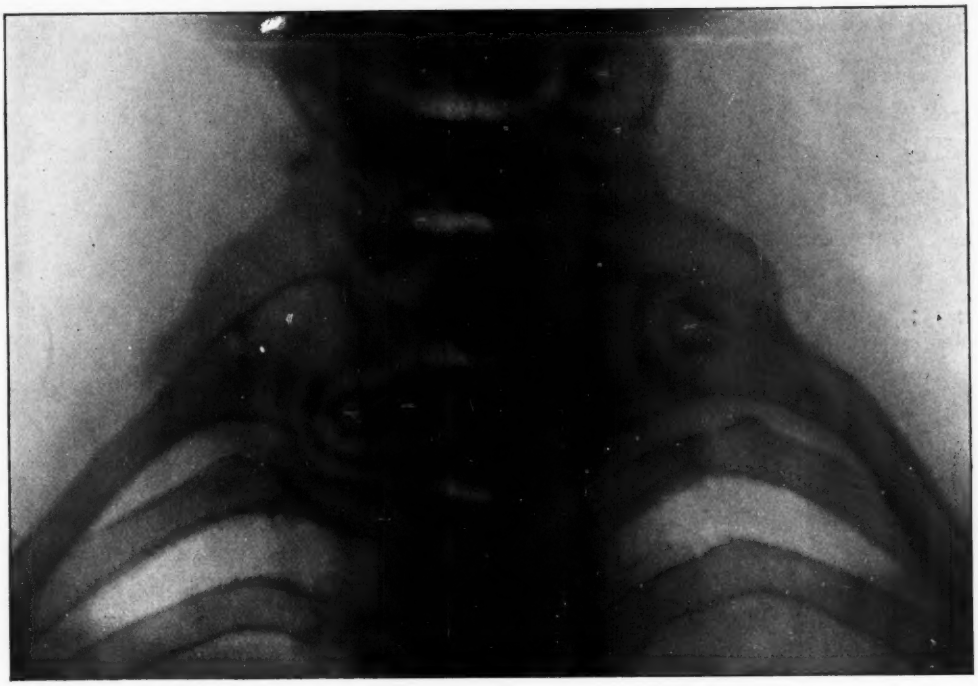

FIG. 1

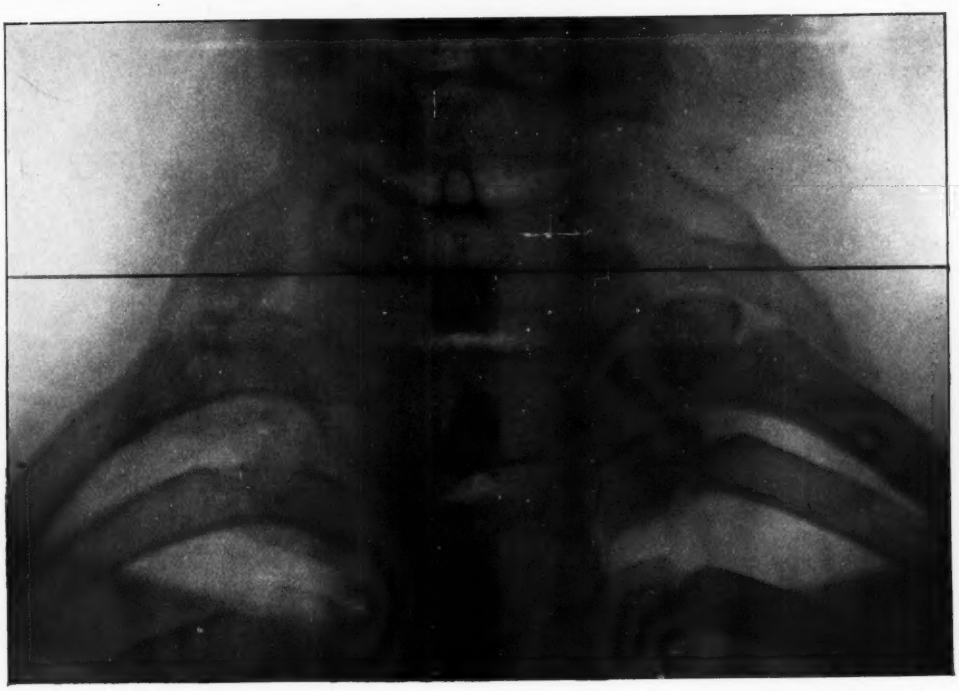

FIG. 2

FIG. 3

FIG. 4

AN UNDESCRIBED FORM OF DWARFISM ASSOCIATED WITH A SPATULATE CONDITION OF THE HANDS

By J. H. DRYSDALE, M.D., F.R.C.P.

AND

W. P. HERRINGHAM, M.D., F.R.C.P.

With Plates 28–31.

It has happened to both of us within the last few years to see cases in which a peculiar deformity of the hands was linked with a dwarfed condition of the body. As we have been unable to find any published account of cases resembling them, we think it worth while to record them here.

They show, at least, a superficial resemblance to achondroplasia, and no doubt have sometimes been classed as examples of that condition, though we are not able to point to any published cases in which this has been done. They show, however, certain important differences and we venture to think they should be classed apart.

Achondroplasia is due to a congenital affection, arising between the third and sixth months of intra-uterine life, of some of the bones laid down in cartilage (the membrane bones escape), whereby certain deformities of the skeleton are produced leading to well-defined and obvious departure from the normal outward and bodily form. As the morbid condition ceases at the sixth month those parts of the skeleton in which the centres of ossification appear later escape deformity, though there is some evidence to show that the disease may be prolonged in some cases for a short time after birth.

The three most characteristic manifestations are: (1) The shape and size of the head. (2) Shortness of all four limbs. (3) The shape and size of the hands. In conjunction with these there is a normal development of the trunk, but owing to the shortness of the lower limbs, and notwithstanding the average size of the body and head, the subject is a dwarf.

Maud, Laura and Amy R., three sisters, first came under the observation of one of us in 1896, and were at that date aged thirteen, eleven, and seven. Three elder children, all males, are normal in every respect and of more than average height. Between the birth of the brothers and the sisters two other children were born dead but no evidence is forthcoming whether they were or were not normal in shape and size.

[Q. J. M., Jan. 1908.]

There is no history of any similar deformity in the family nor of anything likely to be mistaken for it.

They were brought to St. Bartholomew's for 'bending of the legs', and the eldest child had in fact an osteotomy performed on both sides for this deformity.

The mother states that the legs of all the children were quite straight at birth, but in each case began for the first time to bend about the age of five or six.

The photographs 1 and 2 show better than any description the general appearance of the children.

All are short for their age—44 inches, 38¼ inches, and 34¼ inches, instead of the average 57, 53½, and 44 for their respective ages.

In each case the head is large, the vault being well developed, the forehead prominent, and the parietal eminences well marked. The nose is flattened, though the bridge is not deeply depressed in the manner seen in cases of achondroplasia.

The upper limbs are of normal proportional length, and the arm and forearm, thigh and leg also show a normal relation to each other. In achondroplasia not only are the limbs short but the proximal segments in each limb, that is to say, the humerus and the femur are relatively shorter than the distal (rhizomélique, Pierre Marie). In the photographs it can be seen that with the arms hanging by the side the finger-tips reach a point on the thighs almost if not quite as low as in a normal person. Any deficiency in this respect is fully explained by the extreme shortness of the hands. In achondroplasia, on the other hand, when the arms are held in a similar position, the finger-tips seldom reach as low as the level of the great trochanter and may fall considerably short of it. So far as the lower limbs are concerned they also are not short as in achondroplasia. The curves present, however, are great enough to lessen somewhat the distance of the trunk from the ground, and cause the umbilicus to fall rather below the mid-point of a vertical line drawn from head to foot. In achondroplasia the shortness of the lower limbs displaces this mid-point as high, or nearly as high, as the ensiform cartilage.

The hands are extraordinarily short, broad, and fleshy. In achondroplasia the hands also have these characteristics, but the increased bulk of the soft parts, as well as the increased thickness of the phalangeal shafts, does not reach beyond the proximal phalanges, so that the fingers are conical in shape, and when the hand is held with the proximal phalanges closely approximated the two distal phalanges remain separated and present the appearance called by Marie 'la main-en-trident'. In the cases under consideration—as seen in Fig. 3, and better still in Fig. 4—this appearance is entirely absent, the excess of the soft and bony parts is continued up to the end of the fingers, and when the proximal phalanges are closed on one another, the distal phalanges are also in contact, giving the hand the appearance of myxoedema rather than achondroplasia. In addition, the finger pulp projects well beyond the end of the nails, which are raised so as to form an angle with the dorsal surface of the distal

phalanx at the point where the nail-bed is situated. The feet show similar changes. At the junction of the shaft and epiphysis at the wrists and ankles there is a considerable enlargement, and a similar condition, though only to a slight degree, obtains at the junction of the ribs with the costal cartilages. These points are not well seen in the photographs.

Skiagrams of the hands show a marked delay in the appearance of the centres of ossification. Comparing them with those taken from normal children, the centres visible correspond in the child of seven (Fig. 5) to those seen in a normal child of two or three and in some respects are even less advanced, while the child of thirteen (Fig. 7) corresponds to the normal child of between seven and ten.

The epiphyses of the metacarpal bones and phalanges normally begin to ossify between the third and the fifth years. In the skiagram of the child aged seven, no epiphyseal ossification can be seen except the distal centres for the heads of the metacarpal bones of the fingers. In the skiagrams of the other children, though the centres have for the most part appeared, the extent of ossification is in each case much less than in normal children of the same age.

The intelligence of all the children is fully equal to the average.

All three children were treated with thyroid extract, thymus extract, mercury and potassium iodide, and by anti-rachitic measures for long periods without any appreciable result.

The youngest child, now a young woman of nineteen, was seen recently, and except for a growth in height of some eight inches shows hardly any outward change. She now measures 42 inches in height. The circumference of the head is $22\frac{1}{8}$ inches and the face retains a rather childlike appearance. The hair is fine but not thin, the skin natural. The patient is extremely sensitive as to her condition, so that a complete examination was rendered impossible. Fig. 4 shows the present condition of her hands.

The second girl died suddenly at about the age of twenty as the result of a cerebral haemorrhage, a post-mortem examination being made and an inquest held. Unfortunately our knowledge does not go beyond these facts.

The eldest girl is alive but was not seen. The mother states that she remains a dwarf. The bending of the bones has remained stationary for some years.

The sexual functions and development of all three girls were normal.

During this year, 1907, one of us was called to see a patient in Queen Charlotte's Hospital for suspected myxoedema. It proved to be a case of this kind.

Mrs. P. (Fig. 8), aged 30, was delivered at seven months owing to a lateral contraction of the outlet of the pelvis.

She was a dark woman with a well-shaped head and rather prominent nose. Her height was only 4 ft. 2 in. (127 cm.). There was a marked lumbar curve when standing, but no other curvature in the spine. The chest was somewhat rachitic. There was slight genu valgum.

The feet and hands were very remarkable, being fan-shaped, or triangular, and extremely short for their breadth. The upper parts of the limbs were, however, natural for the size of the patient, and the tips of the fingers reached well down the thighs as in the normal woman.

The following measurements were taken :—

	inches	cm.
Tip of olecranon to styloid process of ulna .	9	22·5
Wrist joint to tip of middle finger . . .	6	15
Circumference round hand at the head of the metacarpals, excluding the thumb . .	7½	19
From metacarpo-phalangeal joint to tip of middle finger	3½	9
Head of tibia to tip of internal malleolus .	13½	34
Edge of heel to tip of great toe . . .	8	20
Circumference round heads of metacarpals .	8¾	22

The lower ends of the ulna and radius were remarkably large, projecting almost as if there had been a Colles's fracture. The carpus and metacarpus were small. The fingers were stumpy and very thick, blunted so that the nails were very short, and held fan-fashion spreading from the carpus. The position shown in the photograph is, however, artificial, and is due to the fact that she is holding the cloth in position.

There was no abnormality about the lower ends of the tibia and fibula. The toes, like the fingers, were very short and stumpy.

There was no clubbing of either toes or fingers.

In achondroplasia, the pelvic diameters are much altered from the normal, the true conjugate sinking even as low as 2 inches or under; this though the trunk is of natural size. But in this woman, with the exception of the transverse diameter at the outlet, the measurements, which have been kindly supplied to us by Dr. Stabb, are natural :—

Interspinous	8¾ inches
Intercristal	10 „
External conjugate . . .	11 „
True conjugate	4¾ „
Transverse at outlet . . .	3 „

She stated that she was the only short person of her family. Her brothers and sisters have natural hands.

She had had no previous illnesses, and had, so far as she knew, been in her present condition all her life. We regret that the humeri and femora were not measured, but can state that they were relatively as well-developed as the bones of the forearm and leg.

In the absence of any opportunity for an examination of the affected structures, it is impossible to say much about the probable nature of the disease. With cretinism, except for the low stature, it has nothing in common.

There is an entire absence of the cretinous look, and the mental condition is in no way dull. In addition, all the young patients were treated for some months with thyroid extract without any improvement taking place. The absence of the shortened limbs, the lesser differences in the face and hands, the yielding of the bones at the age of five, seem to separate it from achondroplasia. It seems, if one may judge from the skiagrams, not to be, at all events entirely, a fault of ossification, but rather a delayed appearance of this process. Whatever the cause, or whatever the nature of the lesion, all the bones, at whatever age ossification begins, and whether they be laid down in membrane or in cartilage, appear to suffer, with the exception of the bones of the vault of the skull.

FIG. 1

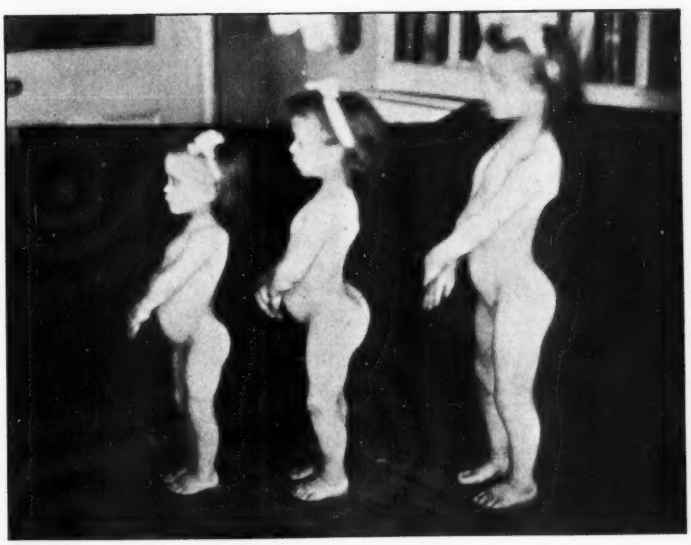

FIG. 2

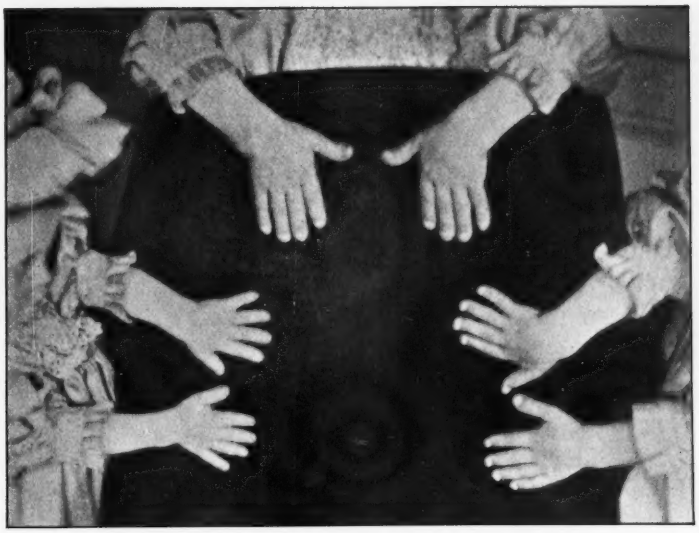

FIG. 3

FIG. 4

FIG. 5

FIG. 6

FIG. 8

FIG. 7

ON OCHRONOSIS

REPORT OF A CASE

By EDGAR REID, M.R.C.S., L.R.C.P., Assistant Surgeon
Swansea Hospital.

THE CLINICAL FEATURES

By WILLIAM OSLER, M.D., F.R.S.

THE URINE

By A. E. GARROD, M.D.

With Plate 32.

Ochronosis is an affection of such extreme rarity that no apology is needed for calling attention to the following case:—

Mrs. T., widow, aet. 67, was admitted to the Swansea Hospital, on June 15, 1907, complaining of a large ulcer on each leg; she showed patches of dark pigmentation in the eyes and ears, and had been passing urine of a black colour. These symptoms were recognized to correspond with those presented by the patient who came under Dr. Pope's care in Leicester Infirmary in 1895: an excellent report of that case, with coloured plates, appeared in the *Lancet* of Jan. 6, 1906, and was reproduced in the *Medical Annual* of 1907.

Family and personal history. No similar condition is known to have existed in any of her relatives. She has borne five children. She has never been troubled with varicose veins or bad legs during her pregnancies. With the exception of her ulcered legs she has always considered herself a strong and healthy woman.

About thirty years ago, and some few years after her last confinement, she was admitted to the Swansea Hospital under the care of Dr. Latimer, suffering from large ulcers of the legs. They healed in a few weeks' time, but shortly afterwards broke down again. The ulcers spread, became very painful, and have never since shown any signs of healing. Carbolic oil (1 in 20) was found to give greater relief from pain than any other of the many applications that she tried, so that for nearly thirty years she has applied strong carbolic dressings twice daily to raw surfaces of some considerable extent.

Six years ago she first noticed that the whites of her eyes and her ears were turning black. For about eighteen months before admission she noticed

that her urine was occasionally black. At times it was passed quite black 'like soot', at other times it only turned black some hours afterwards.

During this period the urine was, she thinks, of a natural colour more often than it was dark. She noticed nothing unusual in regard to the amount or the frequency of micturition.

Condition on admission.

The skin of the face, neck and hands has a decidedly sallow tint compared with the covered parts of the body. There is a small naevus on the lower lip. There is a small patch of xanthoma on each upper eyelid.

Eyes. There are two patches of pigmentation in each eye situated laterally in the sclerotic midway between the corneal margin and the inner and outer canthus when the eyes look straight ahead. Each patch has irregular edges and is circumscribed by a zone of normal sclerotic. There are prominent blood vessels running laterally from the periphery of the globe to each pigmented area. The pigment varies in colour from a blue-black at the circumference to a brown-black in the central parts (the colour here being evidently due to the freer vascularization). The portions of the globe above and below the cornea are quite free from staining and are of that transparent bluish colour often seen in old age.

The ears. Both ears show a large area of pigmentation which, seen from the front, involves the conchar concavity of the antihelix, leaving the tragus lobule and helix free. The colour is a deep slate-blue, especially dark at the prominent ridges which border the concha. The staining of the left ear shows this posteriorly. The skin is not involved, the pigment evidently lying in the cartilages.

The hands. The extensor tendons, as they pass subcutaneously over the metacarpo-phalangeal joints are of the same venous blue colour as the surrounding superficial veins. With clenched fist the knuckles show just a suspicion of blue. There are small varicosities of the vessels about the palmar surface of the fingers.

The feet. No pigmentation is to be seen. The cartilage of the nose is not stained. The ribs are too well covered to be seen. There is no staining around any of the large joints. Her muscles are soft and her gait unsteady owing to her long residence in bed. The reflexes are normal.

At the lower and middle third of each leg there is a large ulcer some 5 or 6 inches long, on the left side completely surrounding the limb, but on the right leaving a small bridge of skin posteriorly. Each ulcer is shallow, the edges look healthy and clean cut and are neither undermined nor unduly prominent. The surface is an angry red covered with small sharp granulations; there is little discharge and no offensive odour. The ulcers bleed readily and are acutely painful to pressure.

Urine. On admission a careful examination was made by Dr. Florence Price. Sp. gr. 1010, pale amber, acid; no albumin or sugar; no blood, pus,

or other deposit. A microscopic examination of the centrifugalized deposit showed a few squamous epithelial cells, white corpuscles, and amorphous urates. The urine did not change colour on addition of alkalies or after standing for 48 hours.

The urine has been carefully watched daily for more than 5 months with only negative results, no discoloration or other abnormalities have occurred, the specific gravity has varied between 1010 and 1024, the most constant figure being 1020.

Shortly before admission, when she first came under my care, I made a hasty and superficial examination of a specimen of her urine. It was of a dirty black colour with no suspicion of green, it became darker on standing and contained a substance which with heat reduced the copper of Fehling's solution. Unfortunately a more careful analysis was postponed until I could avail myself of the facilities afforded by a hospital ward, a delay which I have had ample cause to regret. For, as I have already pointed out, the urine has, since her admission on June 15, displayed no pathological changes and this in spite of every attempt we have made to place our patient under conditions precisely similar to those prevailing at her own home. The strength of the carbolic oil has been increased from 1 in 20 to 1 in 15, and for a time the dressing was procured from the same source as she had herself obtained it for very many years.

At the time of writing these notes, i.e. five months after her admission to hospital, there is a noticeable improvement in the colour of her face; the sallow tint has to a great extent disappeared, the staining of the ears is certainly less intense, and there is some diminution in the pigmentation of her eyes. The carbolic dressings have been continued, and the ulcers are steadily healing, so that now the absorbing raw surface is barely half what it was. The patient is bright and cheerful, and expresses herself as feeling quite well.

Summary. The fact that the last three cases reported, viz., Pope's (1), L. Pick's (2), and the present case, each have a history of many years' association with carbolic acid; makes it impossible to deny that the staining of cartilage and fibrous tissue typical of ochronosis can be produced by the absorption of phenol in small, but long-continued doses. This assumption is further strengthened by the fact that in this patient the staining of skin and other parts has obviously decreased as the ulcers have healed, and the absorption of the carbolic diminished in quantity.

Another point of interest is that the pigmentation has selected those parts of the body exposed to light—thus the hands, face, and neck alone are of a dusky hue; the cartilage of the ears is affected, while that of the nose escapes; the sclerotics are stained only in the more exposed parts; the extensor sheaths of the hands are stained, while those of the feet are free of pigment.

I can think of nothing to explain the abrupt manner in which this patient, on admission to hospital, ceased to pass the dark urine; the fact is interesting, but none the less deplorable from a scientific point of view. Dr. Garrod,

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however, has analysed the urine from time to time, and he is able to assert that the specimens give ample evidence of a slight carboluria, although insufficient to reduce the copper in Fehling's solution, or to show the ordinary tests for hydroquinone.

Our thanks are due to Prof. Osler, who saw the case at the hospital, and Dr. Garrod for the great personal interest they have taken in this patient, and for their kindness in adding the following notes. I am indebted to Mr. H. A. Chapman, of Swansea, for the picture from which the accompanying plate has been produced.

THE CLINICAL FEATURES OF OCHRONOSIS.

In a majority of the cases there are no symptoms directly associated with the staining of the cartilages and fibrous tissues. There is nothing in the anomaly of nutrition which either impairs health or shortens life. The three things for which patients consult a medical man are, the condition of the urine, which easily excites attention, the disfiguring pigmentation of the face and ears, and the associated arthritis.

In the alkaptonuric group the presence of a *copper-reducing substance in the urine* has not infrequently led to the diagnosis of diabetes. This was the case in two members of the Maryland family which I have described (3). One brother was the first case of alkaptonuria recognized in the United States. He had applied for a Life Insurance, and Dr. Barton Brune determined the presence of a copper-reducing substance in the urine. For a time he was supposed to have diabetes, but in conjunction with Professor Marshall, of the University of Pennsylvania, Dr. Brune worked out the nature of the substance in the urine, and the man was accepted as a good life. The brother, whose case I have reported fully, had been an active politician and business man, and in the year 1894, came to Europe for a prolonged rest. He had cardiac arrhythmia, and his Paris physician found a copper-reducing substance in the urine, and told him he had diabetes. He took the Carlsbad cure, and subsequently came under the care of a Berlin physician. He became very much worried over his condition as the supposed diabetes persisted. He was referred to me by his London physician. At first I, too, had no doubt at all as to the question of a glycosuria, but in a short time Dr. Futcher determined that the case was one of alkaptonuria. Now that the knowledge of this condition is so much more widely diffused, there is not the same likelihood that this mistake will be repeated.

In the group of cases with carboluria, to which Dr. Reid's patient belongs, there is still less chance of mistake now that we recognize that ochronosis may be present.

The pigmentation. This it is which gives the characteristic feature to ochronosis, and it was the blackening of the cartilages that suggested to Virchow the name. We now know that it is not only in alkaptonuria that this pigmentation may occur, as in the case here reported it has been associated with carboluria. The staining is very widely diffused, involving all the fibro-cartilaginous structures, and even the coats of the arteries and the endocardium. Clinically, the pigmentation is evident in the sclerotics, the skin, and in the thinner external cartilages and tendons.

The pigmentation of the eyes is very characteristic, and is very well shown in the annexed plate. The staining is in the sclerotic, in the exposed portion, in either a semilunar or a v-shaped patch on either side. In none of the cases has all of the exposed sclerotic been involved, but there has been a clear part between the corneal margin, and another between the pigmentation and the inner or outer canthus. In one of my cases, under observation for nearly ten years, there was a progressive increase in the extent of the pigmentation, but here, too, it has not involved all of the exposed parts. In one instance there was a small patch beneath the upper eyelid. In another there was slight staining at the margin of the cornea. The colour varies from a deep brown to a jet black.

This type of pigmentation of the eyeball is almost pathognomonic of ochronosis. It differs from the pigmentation of the conjunctiva seen in the negro, and occasionally in Addison's Disease. Moreover, in all the reported cases it has, I believe, been symmetrical. A local spot of pigmentation is occasionally met with on the sclerotic without any obvious cause. Such an instance I saw in a young girl of eighteen or nineteen, to whom the spot of jet black pigment in the sclerotic on the outer side of the left eye was a source of great annoyance.

Pigmentation of the skin. In only a few cases of ochronosis has the skin been affected. In Dr. Reid's case here reported there is no involvement. In one brother of the Maryland family the skin presented a very remarkable appearance. Over the nose and cheeks, in a distribution very like that of lupus erythematosus, the skin had a coal-black colour. I thought at first that it might be due to comedones, very thickly set together, but I soon found that it was an intense melanosis of the skin itself. The line of pigmentation over the nose was narrow, and then widened as it passed to the cheeks and extended over the malar bones and along the zygomata. The extent of the staining has increased within the last few years. There was no thickening of the skin, which could be picked up easily. He has also at present, Dr. Futcher tells me, a commencing pigmentation of the back of the hands. The character is very remarkable, quite unlike any ordinary pigmentation, either the brown discoloration of Addison's Disease, or the steel-grey staining of argyria. It is like a pure melanosis, just as if a patch of the blackest negro skin had been inserted. Neither this man's brother, nor sister, nor son, all of whom had alkaptonuria, presented any change in the skin. The extent to which the

pigmentation may occur in the cases associated with chronic carboluria is well illustrated in the case reported by Dr. Pope. The face was uniformly pigmented, and of a deeper colour than the deepest Addison's Disease. While the face was chiefly involved, there was also staining of the hands, particularly the palmar surfaces.

Even when widespread, the staining of the cartilages and fibrous tissues is only visible in certain situations. By far the most characteristic, and in a situation that at once attracts attention, is the pigmentation of the ears. This is very well shown in the plate in Dr. Reid's case. The staining is of a blue-black or leaden colour, very like that produced by dilated veins. It is deepest in the concha, and extends along the antihelix. In certain positions, and when the light falls into the ears, the colour is very striking. It was present in three of the four alkaptonurics in the Maryland family. It also occurred in Dr. Ogden's patient in Milwaukee. I have not noticed the pigmentation of the cartilage of the nose or of the larynx, nor of the eyelids, though these are situations in which it should readily be seen in advanced cases. The staining of the fibrous tissues and tendons is best seen about the knuckles, the knees, and the tendons of the feet. When the patient makes a fist, the knuckles stand out a steel-grey colour, and the same tint may be seen along the tendons.

Arthritis. Four or five of the reported cases have had chronic arthritis. The two brothers of the Maryland family also had for years irregular joint troubles, but the most remarkable feature was the gait, characterized by a slight bend or incline forward of the trunk, and a curious waddle in walking, a sort of 'goose gait'. With this I could never determine any definite lesion of the hip joint itself. The cases reported, which have been tabulated by Pope (1), show that the patients have been the victims of a variety of maladies, particularly tuberculosis, arterio-sclerosis, heart disease, and, in the carboluria cases, chronic ulcer, treated for a period of many years with carbolic acid lotions. A full discussion of the relation of ochronosis to alkaptonuria and other conditions will be found in L. Pick's papers in the *Berliner Klinische Wochenschrift*, 1906, and is considered in this number by Dr. Garrod.

THE URINE IN OCHRONOSIS.

In the appearance of the affected tissues, and in the distribution of the staining, cases of ochronosis resemble each other very closely, but they differ widely as regards the presence of abnormal pigment in the urine; so much so indeed, that the conclusion can hardly be avoided that even the few recorded examples of this very rare condition fall into distinct groups, and that the blackening of the cartilages and other tissues, which constitutes ochronosis, may result from several different causes.

It must be confessed that our knowledge of the urinary changes is still

so imperfect that no definite statements are yet warranted. The known facts merely suffice to indicate profitable lines of investigation to be followed in future cases.

Now that the recognition of the characteristic pigmentation of the ears, sclerotics and skin, which usually accompanies the blackening of the deeper structures, has rendered possible the recognition of ochronosis during the lifetime of the patients, far better opportunities are afforded for a systematic examination of the urine, than when the diagnosis could only be established at a post-mortem examination; and we may reasonably hope that such an examination will be carried out in any suspected case.

In the accounts of some of the recorded examples (4, 5, 6), no mention is made of any peculiarity of the urine, and we may infer that in these cases there was no pigmentary anomaly sufficiently obvious to attract attention.

In nine cases, including that here recorded, the excretion of dark urine, or of urine which became black on standing, has been described as a continuous or intermittent phenomenon. Three of these were well authenticated cases of alkaptonuria, and although in none of them has the staining of the cartilages been verified post-mortem, the identity in character and distribution of the visible pigmentation with that observed in verified cases of ochronosis leaves practically no doubt as to their nature; especially as in a case recorded by Pick, a diagnosis made during life, on precisely similar grounds, was fully borne out at the autopsy.

In two other cases in which the cartilages showed the ochronotic staining post-mortem, there was strong reason to suspect that the patients were alkaptonurics, although the authors who described them were unable to satisfy themselves completely on this point. In both instances the quantities of urine available for chemical investigation were very small. In Albrecht's case (7), the urine blackened on standing, reduced Fehling's solution, and also reduced ammoniacal silver nitrate solution in the cold. Zdarek's (8) search for homogentisic acid was carried out upon only 20 c.c. of urine removed from the bladder after death, and his failure to obtain crystalline lead homogentisate from so small a specimen does not appear to me to afford conclusive evidence of absence of the acid in question. In Clemens's case (9), which is very briefly reported in a discussion at the Congress für innere Medicin at its last meeting (April, 1907), only half a litre of urine was available, as the moribund patient passed everything under him. The behaviour with Trommer's test, viz., the appearance of a brown colour even before heating, and independently of the separation of cuprous oxide, which Clemens regarded as unlike that of an alkapton urine, is in my experience a constant appearance with such urines, as also is a distinct darkening with Nylander's test, not due to reduction of bismuth, but to the action of the hot alkaline reagent upon homogentisic acid.

Clemens obtained a crystalline lead salt of an abnormal acid, but his analytical results were not such as were to be expected if the product were lead homogentisate. Nevertheless, it is at least possible that further investi-

gation, had more urine been available, might have shown that this was really a case of alkaptonuria.

However, the possibility cannot be wholly excluded that under certain conditions urine is excreted which closely resembles alkapton urine in its properties, but in which the abnormal ingredient is not homogentisic acid, but some closely allied substance. Both Albrecht's and Clemens's patients were in the last stage of tubercular disease.

Von Moraczewski has described a case of alkaptonuria which apparently developed towards the end of life in a patient dying of tubercular disease. A lead salt was obtained from the urine, and the acid isolated therefrom had the correct melting point of homogentisic acid. In the record of the autopsy, no mention occurs of blackening of the cartilages, which could not have escaped notice if present. Fürbringer also described the autopsy on an alkaptonuric, and, here again, no mention is made of pigmentation of the cartilages.

It will be seen, then, that of 14 cases of ochronosis recorded, three have occurred in well authenticated alkaptonurics, and in two others alkaptonuria was strongly suspected. In no case of unquestionable alkaptonuria has the blackening of the cartilages yet been demonstrated post-mortem, for in the two cases in which such demonstration was possible, the presence of alkaptonuria was not established beyond possibility of doubt. Nevertheless, in spite of the difficulty of explaining the oxidation of homogentisic acid within the tissues, it can hardly be doubted that alkaptonuria is a cause of ochronosis, although it seems certain that it is not the only cause.

In three other cases, excluding the present one, black urine was passed over long periods, but all the evidence available points to there not having been cases of alkaptonuria. In Hansemann's case (10) there was a history of the excretion of black urine for no less than eighteen years. Salkowski, who examined the fresh urine, found that it gave none of the reactions of melanuria, and Langstein (11), who only had the opportunity of examining a specimen which had been kept for some years, could find no evidence of the presence of homogentisic acid, and considered that alkaptonuria could be definitely excluded. He anticipated the objection that during the long keeping the homogentisic acid might have been destroyed, but I may mention that I was able to recover this acid from some specimens of alkapton urine which had been kept for eight years, which were perfectly black, and alkaline in reaction.

In Hecker and Wolf's case (12) dark urine had been passed at intervals for eleven years. The urine varied in colour, and darkened on standing, but only specimens which had a brown tint when passed became actually black. Addition of ferric chloride caused immediate blackening, just as with true melanuria, and other oxidizing agents produced a similar effect. The urine did not reduce Fehling's solution, and alkaptonuria was obviously excluded. This is the only instance in which the dark urine associated with ochronosis has been shown to give the characteristic reactions of melanuria. In cases of melanotic sarcoma with melanuria, pigmentation of the cartilages has not been

met with, but in such cases the period during which melanogen is circulating in the blood is usually short.

The two remaining cases appear to form with the case here described a definite group. In all three instances ulcers on the leg had been treated for many years by the application of strong solutions of carbolic acid, and it is difficult to avoid the conclusion that this was the actual determining cause of the ochronosis.

In Pope's case the ulcer had existed for twelve years. The surface pigmentation was extreme as the picture of the patient well shows. The urine was almost black, gave a dark brown precipitate with liquor ferri perchloridi and a slight white precipitate with bromine water. No sugar or other copper-reducing substance was present. The colour varied in intensity, and was attributed at the time to carboluria.

Pick, whose case resembled Pope's so closely that the picture of the one patient might be taken as a representation of the other, attributes the ochronosis in both to the application of carbolic acid, but the urine in his case showed no darkening, and Langstein (13), who examined it, was able to exclude both melanuria and alkaptonuria.

In attributing the ochronosis in these cases to a mild form of carbolic acid poisoning, with the circulation for years of small amounts of phenol and its derivatives, Pick does not suggest that the cartilage pigmentation was due to hydroquinone derivatives themselves, but to melanin formed from such substances by the action of a tyrosinase.

It is unfortunate that in the present case the blackening of the urine, which had previously been present, was wholly absent during the patient's stay in hospital, but it is a suggestive fact that it ceased with the discontinuance of the carbolic application. No sufficient evidence is forthcoming as to the nature of the pigmentation, but at that time the urine had a slight reducing action, as in carboluria. A specimen passed in hospital which I had opportunities of examining, did not darken on standing, even when ammoniacal decomposition had set in. All the reactions of melanin and of alkapton urines were wholly wanting. Dilute ferric chloride solution gave neither the transient blue colour of alkaptonuria, nor the blackening of melanuria. The urine did not reduce Fehling's solution. In a second specimen sent after the carbolic application had been resumed, but when the ulcers on the leg were nearly healed, the aromatic sulphates amounted to over 85% of the total sulphates, and the urine had a slight smoky tint.

It will be seen from the above summary that whereas the nature and origin of the urinary pigmentation in some cases of ochronosis remains obscure, there is good reason to believe that in one group of cases the ochronosis is due to the metabolic error which is known as alkaptonuria, and in another has its origin in the local application of carbolic acid extending over many years.

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PLATE 32.

Case of ochronosis showing pigmentation of the sclerotics and the cartilages of the ears.

CRITICAL REVIEW

RECENT WORK ON MEDITERRANEAN FEVER

By J. W. EYRE, M.D.

Mediterranean Fever in its acute phase is seldom seen in this country, except as an isolated instance due to laboratory infection, but in its chronic stages it is only too familiar to those whose duties bring them into touch with members of our sea and land forces. Yet the importance of its bearing upon our national economy is beyond question. The bulk of the cases occurring in our navy and army have in the past been directly traceable to infection contracted in the island of Malta—a spot of immense strategic importance, the head quarters of the Mediterranean Fleet and garrisoned by a military force of some 8,000 strong. If figures are necessary to emphasize the point we may state that no less than 2,229 cases, with 77 deaths and an average case duration of about 120 days, occurred in the garrison alone during the seven years 1898–1904, and very similar figures (viz. 2,149 cases with 34 deaths) are recorded in connexion with the Mediterranean Fleet; a total loss to the combined navy and army of at least 75,000 days' sickness per annum.

The disease may be defined as a specific septicaemia, resulting from infection by the Micrococcus melitensis, endemic in certain localities, running an acute, subacute or chronic course of indefinite duration, often lasting for months or even years, and characterized by lack of constant symptoms other than slight or severe pyrexia—continuous, intermittent or remittent—with marked tendency to repeated relapses, during which the symptoms originally present may recur with undiminished severity; accompanied or followed by neuritis (probably toxic) and by certain metastases such as synovitis, parotitis and orchitis.

Our knowledge of the disease as a distinct pathological entity dates from comparatively recent times — although Hughes contends, and in our opinion with ample justification, that it was known to Hippocrates and is described in his 'Epidemics'. Burnett, a naval surgeon, in a monograph published in 1814 and entitled 'Mediterranean Fever, a practical account of the Fever commonly called The Bilious Remittent', certainly describes cases which to those familiar with its clinical aspects are identical with Mediterranean Fever of the present day. The bulk of the contributions to its literature have been supplied by military surgeons serving in Malta, where the Fever, by reason of its heavy incidence on the troops in their charge, has constantly and imperatively

thrust itself on their notice; thus Boileau, Marston, and Duffey described it, under various names, in the Army Medical Reports between 1865 and 1872: and shortly afterwards Veale, in the same official publication, insisted on the distinctive and specific character of the disease: but it was not until 1887 that the careful researches of Bruce, which resulted in the isolation of the Micrococcus melitensis, established the causative factor in the infective process.

Bruce's observations received ample confirmation from the results of Hughes's investigations, so that when Wright in 1897 applied the agglutination test to patients' serum, thereby simplifying diagnosis, the study of the disease from the clinical point of view was placed upon a scientific basis.

The identity of the fever in the past has been masked under a variety of names almost as numerous as the symptoms exhibited by the individual cases. From the prevailing type of pyrexia, certain observers have designated it Simple Remittent or Simple Continued Fever; from particular clinical features, Febris Suderalis, Gastric or Bilious Remittent Fever; from its resemblance to Enteric Fever, other observers have called it Intermittent Typhoid, Recurrent Typhoid, Typho-malarial or Faeco-malarial Fever: whilst very protracted cases were often termed Mediterranean Phthisis. Other names, identifying the disease with certain localities in which it was prevalent, were Cretan, Cyprus, Gibraltar or 'Rock', Malta, Mediterranean and Neapolitan Fevers.

Of recent years the tendency has been to apply one of two 'place' names to the disease, and to designate it either Mediterranean or Malta Fever, and each of these titles has in turn received the sanction of the Royal College of Physicians of London in the 'Official Nomenclature of Diseases'—a handbook compiled to assist naval and military surgeons in recording their cases for statistical purposes.

Nomenclature such as this, however, not only implies a restricted geographical distribution and attaches a corresponding stigma to the locality named, but is also inaccurate, for with the advent of modern and more accurate methods of study and particularly with the application of the agglutination test and blood culture methods to the disease, the limits of its distribution have been extended considerably, beyond even the Mediterranean littoral to which it was at one time believed to be restricted, and endemic foci have been found in Central and Northern India, in South Africa and other distant parts of the globe.

According to some the distribution of the Fever is determined by the mean annual atmospheric temperature; thus in the northern hemisphere the disease first becomes endemic at or near the 12° C. (55° F.) isotherm—(north of which only imported cases are to be met with)—and increases in the severity of its incidence up to the 16° C. (68° F.) isotherm, where it is fully established: and possibly the question of temperature will eventually be found to have a distinct bearing on the endemic incidence of the disease.

Place names fail signally in other points also; for instance, they suggest no conception of the character of the disease, or of its etiology. Hughes, who had the social as well as the hygienic interests of Malta closely at heart, advocated

the use of the name Undulant Fever, as indicating the general characters of the temperature in cases of the disease. This term, however, has never met with general acceptance, nor is this surprising, as even a casual contemplation of the charts from say a dozen cases taken haphazard will convince any one that the alternating 'waves' of pyrexia and normal temperature are not sufficiently constant to justify its use, indeed, it would be as reasonable to speak of a relapsing case of typhoid or a chronic streptococcic septicaemia as 'undulant' fever.

Italian workers have applied the title 'Septicaemia of Bruce' (*Setticemia del Bruce*) to the disease with increasing frequency during the past few years, and Trambusti (see *Lancet*, London, 1907, vol. 2, p. 1347) now suggests the general adoption of the name; but a better one in the opinion of the writer (1) would be 'Melitensis Septicaemia', which indicates both the nature of the disease and the infective agent; one, moreover, which follows the present-day tendency to amplify the information contained in the term Septicaemia in every case by the addition of the name of the specific microbe.

The statement by the President of the Royal Society Sub-committee, at the annual dinner in December last, that the work of the Mediterranean Fever Commission might be considered as completed, affords a suitable opportunity for considering the many new and interesting facts now at our disposal in connexion with the disease which formed the subject of investigation. The results of this recent work are the more interesting in that they form a striking argument —perhaps the most cogent that can be adduced—in support of the imperative necessity for the experimental and laboratory investigation of disease, and point as a moral that inquiry conducted upon and restricted to time-honoured epidemiological lines may absolutely fail to bring to light the etiological factors concerned.

As previously mentioned, the exact scientific study of the disease dates from the year 1886, when Bruce, then a Surgeon-Captain in the Army Medical Staff, was stationed in Malta. From the clinical evidence at his disposal and from the microscopical appearances presented by the spleen pulp of a fatal case, he recognized the local fever as a septicaemia, and although bacteriology was a science still in its infancy, Bruce, in conjunction with a Maltese Medical Officer, Carruana Scicluna, attempted the detection and isolation of the bacterium responsible for the infection. Blood cultures upon agar-agar from ten cases of the disease were made without success; but eventually one of these cases died, and Bruce, inoculating culture tubes, within an hour of death, from the spleen pulp, obtained a growth of a hitherto undescribed micrococcus in all (2).

This organism was subsequently obtained from eight more fatal cases, was studied in pure sub-cultivations, inoculated into monkeys, and the disease reproduced in its entirety. Bruce's observations were fully confirmed by Surgeon-Captain Hughes (3), who worked at the disease between 1891 and 1896.

In 1897, Wright, then Professor of Pathology in the Army Medical School at Netley, turned his attention to a study of the disease, and in the course of his experiments ascertained that agglutinins were present in the blood serum

of infected and of immunized animals, comparable to those already described by Durham, Gruber, and Widal in connexion with cholera and enteric fever.

Following up this observation with the help of Semple (4) and Smith (5), Wright next demonstrated the presence of these specific agglutinins in the serum of patients who had acquired the disease naturally, and thus placed at the disposal of the clinician a most valuable aid to diagnosis.

For the next seven years little was added to our knowledge of the disease itself, although further details as to its geographical distribution gradually accumulated, chiefly as the direct outcome of the application of the agglutination reaction. Other observations referred chiefly to the clinical aspects of the disease; thus, French workers, among whom may be mentioned Schoull (6), Hayat (7), and Nicolle, studied the blood changes occurring in the course of Mediterranean Fever as seen in Algeria and Tunis, and drew attention to the occurrence of relative, and often absolute increase in the non-granular leucocytes, chiefly affecting the lymphocytes.

Gilmour (8), in 1902, having successfully recovered the micrococcus from the blood of the peripheral circulation in 50 % of a small series examined, in the following year isolated the organism from fluid from the joint in the case of an arthritis of the knee supervening on Mediterranean Fever (9), an observation which was again made by Kennedy (10) in 1904.

Carbone (11), a brilliant Italian worker, who eventually succumbed to Micrococcus melitensis infection contracted in the laboratory, showed in 1904 that in the male guinea-pig purulent inflammation of the tunica vaginalis followed the intraperitoneal inoculation of the Micrococcus melitensis, and, later in the same year, Eyre and Fawcett (12) recorded a case of hepatic and sub-diaphragmatic abscess in man, consecutive to Mediterranean Fever and due to the pyogenetic activities of this micro-organism.

The heavy incidence of Malta Fever on the troops stationed at Malta, and the amount of sickness in the Mediterranean Fleet, at length attracted the attention of the Colonial Office, and it was decided to investigate the disease in a comprehensive and systematic manner. Consequently, in response to the representations of Mr. Secretary Lyttelton, who urged joint action by the Admiralty, the War Office and the Civil Government of Malta, the Mediterranean Fever Commission already referred to was formed in the early part of 1904. The Royal Society having consented to appoint an Advisory Board to supervise the work of the Commission, did so by nominating a sub-committee of its Tropical Diseases Committee, consisting of Col. D. Bruce, C.B., R.A.M.C. (Chairman), Drs. Klein, C. J. Martin, and Sidney Martin, Fleet-Surgeon Bassett-Smith, R. N., and co-opting the writer; stipulating that the selection of investigators should be placed in the hands of the Board. Dr. Ralph Johnstone, whose services were rendered available by the permission of the Local Government Board, Staff-Surgeon Shaw, R.N., Major Horrocks, R.A.M.C., and Dr. Zammit, Board of Health, Malta, were at once appointed as working members of the Commission, and with the assistance of the Chairman, who had proceeded to

Malta for that purpose, initiated the campaign towards the end of June, 1904. Major Horrocks and Dr. Johnstone left Malta at the end of September, and Capt. J. C. Kennedy, R.A.M.C., was appointed to the Commission in addition to Staff-Surgeon Shaw, R.N., and Dr. Zammit, for work during the winter, together with Staff-Surgeon Gilmour, R.N., of the Bighi Hospital Staff, who had volunteered his services. The following May (1905) Major Horrocks returned to Malta and resumed work, and Lieut.-Col. A. M. Davies, R.A.M.C., was appointed to continue the epidemiological inquiries instituted by Dr. R. Johnstone; Col. Bruce visiting Malta, as in the previous year, at the beginning of the summer to ascertain the progress of the work. By the beginning of October, 1905, Lieut.-Col. Davies and Major Horrocks had left Malta, and Staff-Surgeon Shaw, Capt. Kennedy and Dr. Zammit continued the work throughout the winter. In March, 1906, the writer proceeded to Malta and joined Dr. Zammit and Capt. Kennedy. A few weeks later Staff-Surgeon Clayton relieved Staff-Surgeon Shaw, Major McNaught replaced Major Horrocks, and Majors McCulloch and Weir replaced Lieut.-Col. Davies, these members of the Commission forming a working party which remained on the island throughout the summer; while the Chairman of the Advisory Board, Col. Bruce, again visited Malta, in April, to urge upon the local authorities the desirability of instituting preventive measures.

With this brief notice of the constitution and personnel of the Commission we may proceed to summarize the history of its work; but as no less than seven volumes of Reports have been published, comprising nearly a thousand octavo pages, it is obviously impossible within the limits of the present notice adequately to deal with this immense mass of detail, and it is merely proposed to record the salient features of the investigation and refer readers to the Reports themselves for more precise information.

From the first, the investigations were carried out in two distinct directions, the one bacteriological and experimental, the other following the ordinary paths of epidemiological inquiry; and it is with the former that we are now chiefly concerned. During the first two years of the Commission the different members thereof carried on their work independently, and, except in a few instances, without communicating their results to each other; hence the general concordance of their conclusions may be accepted as evidence of their accuracy. Moreover, as they were chiefly engaged in familiarizing themselves with the biology of the specific micro-organism of Mediterranean Fever, and its pathogenic effects when introduced into the monkey, the early volumes of the Reports deal mainly with experiments extending and confirming the results of earlier workers.

The investigations into the saprophytic existence of Micrococcus melitensis brought out very clearly its hardy character as evidenced by its vitality and longevity, and its vigorous resistance to the lethal action of prolonged desiccation. These results—important from their bearing upon preventive measures as well as their more purely scientific interest—are here tabulated, the number of

days recorded in each case representing the maximum period during which the micro-organism could be successfully subcultivated from the material in question.

	Material infected with M. melitensis	M. melitensis recovered alive after	Observer
Moist	*In water*		
	Sterilized Tap water	50 days	Shaw (13)
	„ Sea water	42 „	Eyre and Stenhouse (14)
	Unsterilized Tap water	72 „	Shaw (13)
	„ Sea water	46 „	Shaw (13)
	In Laboratory cultivation		
	Broth culture	173 „	Shaw (13)
	Agar culture	830 „	Eyre (14)
	Litmus milk	284 „	Kennedy
Dry	*Dried on Fabrics* and other materials		
	Strips of linen, Filter paper, Cigarette paper	21 „	Eyre and Duncan (14)
	Coverslips	16 „	Horrocks (15)
	Yarn	90 „	Eyre and Duncan (14)
	Flannel, Khaki serge	80 „	Horrocks (15)
	Sterilized garden soil	91 „	Shaw (13)
	„ dust	24 „	Shaw (13)
	„ sand	20 „	Horrocks (15)
	„ limestone	51 „	Zammit (16)
	Unsterilized dust	28 „	Horrocks (17)
	„ garden soil	20 „	Horrocks (17)

On the other hand, it was shown that an emulsion of the micrococcus dried upon coverglasses was completely destroyed by direct sunlight, in Malta, after an exposure of less than a couple of hours. Infected fabrics required nearly three hours' exposure under similar conditions to ensure the destruction of the coccus; and still another hour was required when the organism received the protection afforded by a layer of soil half an inch deep (18).

The clinical aspect of the disease as it occurs in man was not neglected, and several workers, Gilmour, Zammit and Shaw, were able to confirm in a strikingly conclusive manner the observations of the first-named, previously referred to, as to the septicaemic character of Mediterranean Fever, by isolating the specific micrococcus from the peripheral blood at various stages of the infection (from the second to the three-hundredth day of disease), just as Durham (19) had previously done in the case of experimental laboratory infections in guinea-pigs and rabbits. Often, however, it was necessary to work with fairly large quantities of blood in order to secure cultivations of the micrococcus; and in some instances the agglutinating power of the patient's serum, which varied from 1 in 20 to 1 in 3,000, in the different cases from which the micrococcus was recovered, is suggested as a factor probably having some bearing upon the relatively large amount of blood required in order to demonstrate the presence of the coccus. Subsequently the writer, by employing the technique usually

adopted in England, was able partly to eliminate this factor and to demonstrate the micro-organism in the peripheral blood in much larger numbers in the three acute early cases examined. The general results are tabulated for convenience of reference:—

Cases examined	Micrococcus recovered from	Maximum number of cocci recorded per c.c.	Minimum number of cocci recorded per c.c.	Observer
16	8	—	—	—
45	38	400	less than 1	Gilmour (20)
103	69	256	less than 1	Shaw (21)
49	27	200	2	Zammit (22)
24	16	—	—	Bassett-Smith (23)
3	3	10,000	1,000	Eyre (24)

Durham had also remarked, nearly ten years before, the discharge of the micrococcus in the urine of the infected guinea-pig, and expressed the opinion that the same phenomenon would ultimately be observed in man. This forecast was shown to be correct by Horrocks, Kennedy, Bassett-Smith and Shaw as soon as they took up the investigation of this point, for they were able to isolate the micrococcus, often in large numbers (e. g. over 1,000 per c.c.) from the urine in something over 50 % of the patients suffering from the disease who were examined at periods varying from the 15th to the 249th day of the disease (see *Med. Fever Reports*, Parts I, III and V).

It must be noted, too, in connexion with these investigations, that while most of the work was carried out upon material collected in Malta, Bassett-Smith's observations refer to material derived from cases of Mediterranean Fever invalided home, subsequent to their arrival in England and admission to Hasler Hospital. On the other hand, these same workers failed to demonstrate the presence of the micrococcus in sweat, scrapings from the skin, sputum, or the faeces.

[With regard to the results of the examination of faeces it may be mentioned that after demonstrating the presence of the micrococcus in the intestinal canal of experimentally infected guinea-pigs, tracing it down from the duodenum to the rectum, and isolating it from the faeces, I was able whilst in Malta to demonstrate the presence of the micrococcus in the faeces removed post-mortem from the colon of a fatal acute case in man (see *Med. Fever Reports*, Part VI, p. 129).]

Following up these lines of investigation as applied to natives of the island, Shaw was able at the end of the summer (Part IV) to make the sufficiently startling observation that an ambulatory type of the disease existed which was to all intents and purposes devoid of clinical symptoms. The subjects of this form of infection, however, yielded a marked agglutination reaction; cultivations of the micrococcus could frequently be obtained from their peripheral blood, and, further, they excreted urine which though normal in appearance contained large

(22,000 per cubic centimetre) numbers of the cocci in a fully virulent condition, and sometimes so many as to be innumerable.

Such briefly are the results obtained which refer to the saprophytic existence of Micrococcus melitensis under laboratory conditions and the clinical relationship of the organism to the disease as it occurs in the human subject.

With this mass of material as a basis, the Commission was now in a position to study some of the paths by which infection was conveyed, and the longevity of the micrococcus in dust—under laboratory conditions—led to a series of experiments by different workers directed to the possibility of infecting monkeys by exposing them, in a confined space, to artificial dust-storms, in the production of which highly contaminated dust and soil were employed; or by blowing infected dust directly into the nostrils. Some of these experiments were successful, it is true, but the majority of the experimental animals remained unaffected, no matter how abnormal the conditions under which they were placed.

Contact of the healthy attendants with patients suffering from Mediterranean Fever appearing, prima facie, a likely explanation of the heavy incidence of the disease upon the nursing portion of the community, experiments were carried out upon the monkey to elucidate this point, but it was soon recognized that if the contact was limited to skin surfaces only and *contamination with infected excreta carefully eliminated* infection never resulted—a result which was quite in accordance with the failure to demonstrate the micro-organism in sweat, sputum, breath or in epidermal scrapings. On the other hand, it was shown that contact of the unbroken mucous membrane of the glans penis of the monkey, for a few seconds, with wisps of cotton wool soaked in infected urine from an ambulatory (human) case, resulted in successful infection; and the routine examination of the prostitutes in Malta afforded strong probability that infection is occasionally conveyed—very rarely perhaps, for the investigations of the epidemiologists failed entirely to trace any of the cases in 1906 to this cause—during sexual congress. In the examinations referred to it was found that just over 30 % (41 out of a total of 140 registered women) gave evidence of melitensis infection by the presence of a specific agglutination reaction. Micrococcus melitensis was isolated from the urine of four of the women, and also from material collected by swabbing the interior of the vagina from one prostitute who although only recently convalescent from an acute attack of the septicaemia, had already resumed her vocation, and from a second who had suffered from a severe attack eighteen months previously.

The organism was also isolated from a similar situation in the case of a married woman, recently convalescent, whose husband however had apparently been infected at about the same time and from the same source as herself.

Simultaneously with the earlier observations other important investigations were in progress. Towards the end of 1904 Zammit, at the instigation of Carruana Scicluna, who still takes an active interest in the experimental work, instituted an inquiry into the possible natural infections of the goat—the most important animal in Maltese domestic economy—by the bacteriological examina-

tion of the spleen in all goats slaughtered in the public abattoir, and the testing of the blood for specific agglutinins. At the same time he took more active steps in the inquiry by feeding agar cultivations of the micrococcus to some selected healthy goats. No constitutional effects were produced, but as specific agglutinations appeared in the blood a month or so later this experiment was repeated, with similar results. A batch of six presumably healthy goats was next purchased as a preliminary to further experiments, but it was found that specific agglutinins were present in the sera of five of the animals. Zammit next proceeded to examine the blood and milk for the presence of Micrococcus melitensis, with the result that the organism was isolated from the blood of two, and (by Horrocks, to whom the specimen had been handed by Zammit for examination) from the milk of one of them. Later, the micrococcus was isolated from the milk of four others of these animals and from the urine also of two of them.

Zammit further noted the appearance of the agglutinins in the milk of the goat, and modified the time and dilution factors of the routine agglutination reaction in order to adapt it to the examination of milk.

All the members of the Commission thereupon engaged in an extended series of observations as to the evidences of infection in the Maltese goat, and, as a result of their inquiries, applied to nearly 1,500 animals, they state that in round numbers some 50 % of the Maltese goats yield a positive agglutination reaction and about 10 % secrete milk which contains the Micrococcus melitensis.

In 1906 a further 637 milch goats were carefully examined, and of these some 15 % gave evidence of infection as shown by the agglutination reaction, and the micrococcus was recovered from the milk of nearly 4 % of the total number. Communications received by the writer from Italian workers, notably Gabbi of Messina, show that the goats of Sicily and of Southern Italy are infected in similar proportions.

As a point of more than passing interest, it may be noted that the micrococcus was isolated in virulent condition from two human cases in which an attack of the Fever had not caused an entire cessation of lactation.

Attention was next directed to the examination of other domestic animals on the island, with the result that definite evidence of Micrococcus melitensis infection acquired naturally was speedily forthcoming.

Animal	No. examined	No. giving agglutination reaction	Observer
Cow	33	10	Shaw (25)
Bullock	31	5	Shaw (25)
Mule	87	39	Kennedy (26)
Dog	160	18	Kennedy and Eyre (27)
Horse	100	46	Kennedy (26)
Cat	22	5	Shaw (25)

The micrococcus was recovered from the milk of two of the cows and was isolated post-mortem from one of the dogs and one of the cats.

As a result of these observations upon the presence of Micrococcus melitensis in the milk of such a large number of the Maltese goats, attention was at once directed to the possibility of the entrance of the micro-organism into the human subject by way of the alimentary tract, and during the ensuing eight months experimental feeding with infected material was practised upon various animals. The exact method adopted varied in different cases. In some, laboratory cultivations were mixed with the food; in others, dust, previously mixed with the infected urine from a Mediterranean Fever patient and dried, was sprinkled over or incorporated with the food, but in practically all the cases the infected food was administered repeatedly at short intervals for a period of time which in some cases extended over many months. A considerable number of goats were treated thus, and the majority of them developed in due time such unmistakable signs of infection as the secretion of milk containing the micrococcus.

Of 24 monkeys similarly fed 75% yielded evidence of the presence of specific agglutinins in the serum, and 66% by the isolation of the micrococcus from various organs post-mortem gave incontrovertible proof of successful infection. In the summer of 1906 the monkey-feeding experiments were modified by the writer and his colleagues in that 28 monkeys were allowed to drink infected milk from open pannikins on one day only, and were subsequently examined at varying intervals after the commencement of the experiment, with the result that 26 (or approximately 93%) elaborated specific agglutinins, and 24 (or approximately 86%) yielded cultures from various organs when examined after death. Two monkeys fed directly into the stomach by means of a soft rubber tube remained unaffected (see *Med. Fever Reports*, Part VI).

Proof such as this of the highly virulent and infective character of naturally infected milk quâ the monkey rendered it extremely likely that this article of food was dangerous, even if not equally so, to man. Evidence of the accuracy of this assumption was ready to the hands of the Commission, for, thanks to the courtesy of Prof. Ruffer and Dr. Gotschlich of Alexandria, and the energy of Kennedy, some particulars of an epidemic of Mediterranean Fever on board the s.s. *Joshua Nicholson* had become public. The details were investigated by Clayton, and the results of this delicate experiment on the human subject, planned and perfected in Nature's own laboratory, confirmed in a striking manner the accuracy of the observations of merely human investigators. The ship in question carried a cargo of sixty milch goats—some of which were subsequently proved to be infected with M. melitensis—from Malta to Antwerp, the voyage lasting just a fortnight. During this time a very large quantity of milk was daily accessible, and many of the officers and crew partook of it. Of 10 individuals who are known to have drunk freely of the raw milk, and whose subsequent movements could be traced, eight fell sick at intervals varying from 18 to 34 days after the commencement of the voyage, and from the presence and intensity of the serum reaction in five of them there can be no reasonable doubt that Mediterranean Fever was the cause of

their illness. The goats finally reached America, and were placed in a quarantine station at Athenea, N.J., for observation, and here a female attendant, who consumed milk from some of the goats, also developed Mediterranean Fever.

Negative evidence, which showed that the absence of Maltese milk from the dietary of our countrymen in Malta coincided with a marked diminution in the incidence of the Fever, also accumulated rapidly, for owing to the persistence of the Commission in 1906 in its attempt to collect samples of milk for examination, and the cooperation of the local sanitary authority by prosecuting goatherds who refused to comply with the law and supply samples to authorized individuals, the Maltese engaged in the milk trade resolved on the heroic course of action and went 'on strike', and refused to sell any milk for human consumption during the latter half of May. The naval and military authorities in response to the urgent recommendations of Bruce were already engaged in formulating plans for the substitution of condensed for goats' milk in the men's dietary, but these had not yet come into force, and judging from the obstacles placed in the way of giving effect to the Commission's recommendations in other directions by departmental red tape, the civilian may be forgiven for assuming that they would not have become effective before the end of the year at the earliest. But being confronted by the sudden loss of a most valuable food for the sick, the local authorities were compelled to take the initiative and to provide a substitute for the goats' milk for more than a fortnight. When the recalcitrant milkmen, ending their 'strike', pleaded to be allowed to resume the supply, they were met with an absolute refusal to reconsider the matter, and tinned varieties of milk continued to be consumed. The effect on the incidence of the Fever was most marked. Dealing with figures relating to the garrison, from January 18 to December 31, 1905, 750 cases of Mediterranean Fever were admitted to hospital; in the year 1906, 144, of which 112 were admitted between January 1 and June 30, and 32 only from July 1 to December 31 (that is to say, after the alteration in the milk supply). During the period of nine months, from January to December, 1907, 7 cases only are recorded as occurring in the Malta garrison.

With regard to the navy, equally satisfactory conditions exist. In 1905, there were 490 admissions for Mediterranean Fever; in 1906, 248 cases, of which 201 occurred during the first half of the year. In 1907, from January 1 to the end of September, there were *no cases of this disease* reported from the Mediterranean fleet.

Additional evidence of similar import has been elicited by Horrocks during his inquiry into the history of Mediterranean (or 'Rock') Fever as it has affected the Gibraltar garrison. The military population of this isolated station has numbered between 4,500 and 5,000 for many years past. In 1884 there were some 429 cases of the fever, twenty years later (1904) there were none—the decline in the number of cases dating from about the year 1887–8. In the first mentioned of these years (1884) the War Office was granting permission to goat

owners to graze some 1,500 goats upon the Rock. In 1887 these grazing passes were reduced in number and applied to about 1,200 animals: further reductions were made in succeeding years until in 1890, 600 goats, and in 1905 only 254 goats were to be found on the Rock. Again, in 1884 practically all the goats were of the famous Maltese breed, belonged to Maltese goatherds, and regular shipments of goats took place from Malta to Gibraltar to meet the demand. These cargoes gradually became smaller and less frequent as the cost of freight increased, grazing passes were reduced, and goat owners relinquished their businesses, and finally ceased entirely. Consequently the 254 goats examined in 1905 were made up of 90 Maltese, 62 Spanish, and 102 'crossed' (that is Spanish dam and Maltese sire) breeds. Of these some 14% by the presence of the agglutination reaction were regarded as giving evidence of recent or remote infection by Micrococcus melitensis, and from the milk of one animal the specific organism was recovered on one occasion.

So conclusively does the evidence appear to me to point to the consumption of infected goats' milk as the most potent factor in the production of Melitensis septicaemia, and so necessary is it to deal immediately with this animal if it is desired to eradicate the disease from what should be one of the beauty spots of the Mediterranean, that I drew up and transmitted to the Advisory Board of the Commission a series of recommendations which were incorporated in Part VI of the Reports. In these, the application of a modified 'Bang' method [for removing an infective disease from herds of cattle] to the Maltese goats is strongly advocated; and seizure of infected animals combined with a system of compensation, provided for.

Much of the systematic work carried out by the Commission produced results of a completely negative character, and need not here be referred to, but the investigations into the possibility of infection through the agency of the mosquito must not be omitted, for even in 1902 Zammit had collected evidence of the epidemiological type which pointed in this direction, and later, Ross had pointed out the probable association of Mediterranean Fever with the salt-water mosquito (Acartomyia zammitii) which is peculiar to the Mediterranean littoral. Then, too, some observations in 1905 by Horrocks, Zammit and Kennedy clearly showed that the common species of mosquitoes (viz. Culex pipiens and Stegomyia fasciata) that are prevalent in Malta undoubtedly act as carriers of the Micrococcus melitensis. Moreover, each of these last three observers records one instance where infection of man, the goat and the monkey respectively, took place apparently through the agency of one or other of these mosquitoes. As, however, in each of these cases the observation was open to hostile criticism, the 1906 Working Party investigated this point further by means of strictly controlled experiments in which mosquitoes of all three of the before mentioned varieties were utilized. Taking advantage of Eyre's previous work on the acutely septicaemic form of Micrococcus melitensis infection in the guinea-pig, in which the organism appears in the peripheral circulation in enormous numbers, the mosquitoes were first fed on infected guinea-pigs, and subsequently at forty-eight hour

intervals on healthy monkeys, the possibility of infection being shown by plating the stomach contents of random samples of the infected diptera at each stage and enumerating the resulting colonies of Micrococcus melitensis. Experiments upon nearly thirty normal monkeys, using mosquitoes in which the alimentary tract was teeming with virulent cocci, resulted in an extremely mild infection in one; and I am quite of the opinion that when infection occurs through the agency of the mosquito it probably does so as the direct result of scratching infected mosquito droppings into the skin puncture. Experiments upon similar lines using a biting fly (Stomoxys calcitrans), which was shown to be a potential carrier, to bite young kids, gave entirely negative results, as did like experiments with rat and dog fleas.

With regard to therapeutic and prophylactic measures, Eyre describes the want of success that attended his efforts to prepare a potent antiserum from the horse; but, on the other hand, the prophylactic inoculation of a limited number of sick berth attendants at the Naval Hospital and R.A.M.C. orderlies with a vaccine prepared from killed cultures of Micrococcus melitensis yielded promising results which should encourage further observations in this direction, while the therapeutic treatment by vaccines of infected goats held out considerable prospect of ultimately successful results. Bassett-Smith (28), too, after an extended series of cases, speaks hopefully of treatment with similar vaccine of the chronic form of the disease in man.

Turning now to the epidemiological inquiries which, however, can only be briefly referred to, it must be remarked that for the first two years of the Commission's existence, the epidemiologists were working to all intents and purposes independently. During this period a mass of valuable information was elicited which will doubtless have an important bearing upon the hygienic progress of Malta in the immediate future, but nothing save negative evidence was elicited with regard to the causation of the disease. Thus Johnstone, in Part II of the Reports, writes, 'The evidence so far as it goes seems to show that food and drink have no marked connexion with the spread of the fever . . . the facts with regard to infection by means of excreted pollution of the hands, the food or the dust in houses, so far as I have been able to deal with them, are suspicious, but they are not sufficiently strong to justify any conclusion'.

Again in Part IV, Davies states, 'the various modes of propagation of the disease that have been suggested by different observers have been considered in order, and, on the evidence of the facts ascertained, a negative conclusion as to their ability to explain the behaviour of this epidemic (i. e. Mediterranean Fever amongst the troops in Malta) has been arrived at in regard to transmission (1) by water, (2) by milk, or other articles of food, (3) by air contaminated with excremental (faecal or urinary) effluvia: *transmission*, (4) *by direct or semi-direct contagion, or* (5) *through the agency of mosquitoes appears from the evidence to be more probable than in any other way*'.

In 1906, however, when the epidemiologists were in close touch with the

bacteriologists of the Working Party, and were kept fully informed of all the results obtained in the laboratory, their inquiries were more productive of positive results, and Clayton, McCulloch, and Weir in Part VII state that 'Inquiries into the milk histories of service patients this year have elicited the fact that, in the large majority of the cases, a direct relation with the use of fresh milk could be traced. The evidence obtained from investigations as to the relative prevalence of Mediterranean Fever amongst the consumers of condensed milk chiefly, and of fresh milk chiefly, have uniformly shown that the chances of infection are much greater in the case of the latter'; whilst, to conclude, it may be mentioned that the recommendations of the epidemiologists, which are almost word for word identical with those set out by the bacteriologists, are prefaced by the significant statement, '. . . the goat is more than probably the primary source of the disease in the vast majority of the cases, if not in all cases . . .'

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THE ASSOCIATION OF PHYSICIANS OF GREAT BRITAIN AND IRELAND

THE SECOND ANNUAL MEETING of the Association will be held in Edinburgh on June 11 and 12, 1908.

Those Members who wish to make communications, or to introduce communications by Gentlemen who are not Members (Rule 18), are requested to give notice to the General Secretary before March 31, stating the title or subject proposed.

All such notices will be laid before the Executive Committee.

W. P. HERRINGHAM,
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LONDON, W.
General Secretary.

A CONTRIBUTION TO THE SUBJECT OF RHEUMATISM BASED UPON A STUDY OF 52 CASES IN CHILDREN UNDER FIVE YEARS OF AGE, AND AN ANALYSIS OF 100 CASES OF FATAL SUPPURATIVE PERICARDITIS IN CHILDHOOD

By F. J. POYNTON, M.D., F.R.C.P.

THERE has been a good deal of difference of opinion expressed by writers as to the frequency of acute rheumatism in children under five years of age. Some have maintained that it is an exceedingly rare occurrence, while others have doubted this. The question is one of theoretical and practical importance, and this is my excuse for putting on record here my own experience as a contribution to the subject of acute rheumatism.

The theoretical interest lies mainly in our conception of the cause of acute rheumatism, or, as I would prefer to call it, rheumatism. If, as one is now almost compelled to admit, there is an infective agent, or, in the opinion of many, more than one, which determines the active disease, it is difficult to understand why, during the first five years of life, the occurrence of the infection should be very unusual. It may be reasonably admitted that prior to school life there is less exposure to the infection, but even then, one can hardly help believing that a sufficient number of cases must be met with to enable us to recognize that rheumatism does not make a mysterious appearance at any particular age, but is throughout life a menace to some constitutions. If this should prove to be the case, it will help us to bring the rheumatic infection into line with such other great infections as the pneumococcic, tubercular, and typhoidal.

In a symposium upon rheumatic fever in childhood, the result of a recent Congress in America, I find one writer has the hardihood to suggest that we in England have manufactured a disease in children, which we call rheumatism, by fitting together all manner of divers symptoms. This procedure, according to him, has been adopted to account for the disease up to the age of twelve years! No one in this country has any qualms as to the reality of the disease from five to twelve years, and this unguarded writing can only be a warning to those who live in a different country and attempt to criticize the clinical acumen of physicians who have special advantages in any particular line of investigation.

There are several points of practical interest. The question of diagnosis is one, for under five years of age such widely different disorders as scurvy, anterior poliomyelitis, spinal caries, congenital syphilis, gonococcal and meningococcal arthritis, congenital heart disease, influenzal and pneumococcic septicaemia come into the field of discussion. This particular aspect of the question I shall not consider here, for it is dealt with in many books, and in a recent paper in the *Edinburgh Medical Journal* (Sept., 1907) I have dwelt upon some of the chief of these difficulties.

Another point is the clinical character of the disease at this early age. Shall we find this unusual, or closely resembling the character in later childhood and adolescence? The death rate, the percentage of cardiac affections, and the liability to relapse, are other details of importance.

Lastly, shall we be led from a study of such cases to the view that rheumatism is not an entity, because we find that at this age its differentiation from other infections becomes so difficult as to degenerate into mere academic hair splitting? Upon this point I have been at some pains to collect for comparison 100 fatal cases of suppurative pericarditis under twelve years, mostly the result of the pneumococcic infection. My object has been to study side by side with rheumatism, which I regard as an entity, an infection which bacteriologically and clinically comes close to it.

There are fifty-two cases of rheumatism in children under five recorded in this paper. Many of the notes are fragmentary, and as excuse I would offer that they are taken from cases and jotted down during the conduct of a very exacting out-patient department, in which frequently as many as 100 patients had to be dealt with in a morning. They have this value, that they are all personal observations, not one is taken from hearsay evidence, and as such they assist in establishing the main thesis of the paper, that the frequency of rheumatism in children under five is sufficient to make one believe that it obeys the laws of other great infections.

To these fifty-two cases are appended seventeen others. These are older children, who have come to me with rheumatism, whose parents have given a history of an earlier attack before the age of five. In the case of chorea, the evidence when repeated in several instances is very suggestive of truth, for chorea makes a deep impression upon the minds of parents. The fifty-two cases, and seventeen presumptive ones, are placed in appendices at the end of the paper, and, in order to avoid wearisome reiteration, the chief points that they illustrate are considered in the short summaries that follow. There can be, I think, no doubt that the fact that I have been able to collect, in a desultory fashion, fifty-two examples of rheumatism under five years, all of which have been under personal supervision, settles the question that rheumatism resembles other great infections in having no mysterious age limit.

It is equally clear that the disease before the age of five years resembles very closely the condition from five years to adolescence, for if we take these fifty-two cases and choose those manifestations of acute rheumatism that are generally

accepted as cardinal, such for example as heart disease, arthritis, chorea, sore throat, and nodules, we find the following figures :—

Definite heart disease	in 43 cases.
Arthritis or arthritic pains	in 35 „
Chorea	in 18 „
Sore throat	in 10 „
Nodules	in 8 „

The mortality is high at this early age. Eight died, and five more were in a hopeless condition. Twenty-two made partial recoveries with permanently damaged hearts, and among these it is more than probable that some succumbed later to further attacks.

A terminal pericarditis was present in seven out of the eight fatal instances, and there were in these cases many other manifestations of rheumatism, the disease generalizing as it does in other infections in childhood. Yet, in spite of the systemic involvement and terminal pericarditis, it was impossible to mistake the condition for any other than rheumatism. In support of this I submit the analysis of 100 cases of suppurative pericarditis in childhood, the great majority of which were pneumococcic in origin. In fifteen of these the bacteriological nature of the condition was accurately ascertained as pneumococcic. Eight were probably not of this nature, being associated with acute osteo-myelitis, otitis media, and suppurating wounds, and in these there were multiple pyaemic abscesses.

One example of a characteristic case will throw into relief the differences in the clinical course of a rheumatic and pneumococcic pericarditis. *A. C.*, a female, aged $2\frac{3}{12}$ years, had suffered for several weeks from whooping cough, followed by pneumonia. When she came under observation she was very cyanosed and dyspnoeic. Respiration was panting, and there was irregular fever. Both sides of the chest showed signs of effusion, and later in the illness the cardiac dullness was found increased, and the sounds were noted to be faint. Double empyema was diagnosed and suppurative pericarditis suspected. Death occurred rapidly, and $1\frac{1}{2}$ ounces of pus were found in the pericardium, together with pus in both pleurae. The pneumococcus was isolated from the effusion. Thus, in this case, associated with this form of pericarditis, there were purulent pleural effusions, but there was no arthritis, and, still more striking, there was no endocarditis.

Rheumatic pericarditis is, on the whole, easy of diagnosis, but few conditions are more difficult to detect than suppurative pericarditis. In only six of the 100 cases was it detected with certainty, and two of these showed the rare symptom in suppurative pericarditis of pericardial friction.

The reasons for the difficulty in diagnosis help us to emphasize the distinctions between rheumatic and pneumococcic pericarditis. Thus the occurrence of friction in 2 % of the latter series is a very different experience to its frequency in the rheumatic form.

The absence of endocarditis is even more remarkable, only 1% of the pneumococcic showed any valvular lesion. Again, in only one of these cases was pericarditis the outstanding lesion. Three others showed evidence of old pulmonary disease. Fifty-four were associated with an empyema on one or both sides, and thirty-one with acute pleurisy or pneumonia. Two were complicated by acute pulmonary tuberculosis, and eight with septic broncho-pneumonia.

Pleurisy and broncho-pneumonia are met with in virulent rheumatic heart disease, but it is quite the exception and not the almost invariable rule for the pulmonary lesions to dominate in the clinical picture.

Couple this with the fact that in an analysis of 150 cases of fatal rheumatism under twelve years, which I made ten years ago, 149 showed a valvular lesion, and I doubt whether two more striking proofs of the specific differences in these infections could be possible.

Nevertheless, if we turn to the age incidence, we find the most convincing additional evidence. In the pneumococcic series 84% occurred before the child reached the fourth year, and 66% between the ages of one and three years. Rheumatic pericarditis, as shown by these fifty-two cases, certainly occurs with some frequency under five, but this frequency rises rapidly, with the incidence of rheumatism, up to the age of ten. Pneumococcic pericarditis followed measles in twelve instances; the rheumatic is more closely associated with scarlet fever.

These fatal cases of pneumococcic pericarditis also bring out clearly that rheumatic pericarditis cannot be looked upon as a peculiar phase of those infections which produce suppuration, using that term in its everyday sense. For if we first consider rheumatic pericarditis we find an acutely virulent haemorrhagic form, a severe form in which occurs an exudation, which is in my opinion a rheumatic suppuration, a mild form with a clear exudation, and, lastly, a smouldering fibrino-plastic one.

If we consider the pneumococcic pericarditis we find the same variety of processes. There are the fulminating types, the severe ones with profuse suppuration, the milder ones with a more fibrinous exudation, and the undoubtedly rare but definite cases in which there is a partial organization of a chronic inflammatory exudation.

Although the difficulty in the diagnosis of suppurative pericarditis is almost insurmountable, and for this reason it becomes a practical impossibility to date the exact time of its onset during the course of an acute illness, nevertheless the post-mortem records show that this pericarditis may last many weeks before proving fatal, and the illnesses associated with this condition may be grouped into three classes:—

1. The acute, running a course of about four weeks. This included twenty cases of my series.

2. The sub-acute, lasting from four weeks to six months. Representing fifty cases.

3. The chronic, with insidious onset, lasting from six months to one year. Representing seventeen cases.

What phase then can rheumatic pericarditis, with all its varieties, represent of the suppurative forms, which themselves show similar variations? The wildest speculations would fail to conceive of any such phase, and the fact is forced upon us that we are dealing with comparable, but parallel pathological processes, which, in the terms of Euclid, if produced to any extent can never meet.

Such clinical and pathological facts as these are, in my opinion, far more convincing evidence of the specific nature of rheumatism than are the evidences of laboratory tests against its specificity, for they represent the behaviour of the infective agent in the media of the human tissues, which, when all is said and done, are the media with which we are concerned in human diseases. In conclusion, I would hold that rheumatism, though unusual, is by no means rare under five years, and that its study strongly supports the specific nature of the infection.

Appendix I.

Fifty-two cases of Rheumatism under five years of age.

Case 1.—Jan., 1899. T. W., male, aged $4\frac{11}{12}$ years. Two weeks previously he had complained of pains in the knees, followed by chorea. When first under observation there was moderate general chorea and early mitral disease. A severe attack resulted, but there was a partial recovery and the child was able to get about again. In November, 1899, there was a severe relapse with fresh cardiac involvement and nodules, with wasting. This case was lost sight of, but the condition was practically a hopeless one.

Summary: Relapsing rheumatism; arthritis; morbus cordis; chorea; nodules; outlook hopeless.

Case 2.—Oct., 1899. E. S., female, aged 4 years. A vague history of some weeks, in which pains in the joints were complained of, and breathlessness noticed. There was a family history of rheumatism. This child had organic mitral disease. A good recovery followed. She was lost sight of.

Summary: Arthritic pains and heart disease; good recovery.

Case 3.—Nov., 1899. M. P., male, aged $3\frac{6}{12}$ years. This child had been living on the ground floor in a damp house, and was brought for chorea, which had been preceded by a sore throat. When first seen there were marked anaemia, chorea, and dilatation of the heart. After an illness of four months there was recovery with a mitral lesion. She was lost sight of.

Summary: Anaemia; chorea; morbus cordis; sore throat; recovery.

Case 4.—March, 1900. G. M., male, aged $4\frac{3}{12}$ years. His father had suffered from rheumatic fever. There was a history of some weeks of debility, wasting, and anaemia, followed by slight chorea. When first under observation there was, in addition, dilatation of the heart. This patient made a good recovery.

Summary: Anaemia; chorea; cardiac dilatation; recovery.

Case 5.—Sept., 1900. J. M., male, aged $3\frac{4}{12}$ years. Some weeks before coming under observation this child was reported to have caught cold and developed a sore throat. There followed multiple arthritis, the ankles being first affected. When I first saw him there were multiple arthritis, profound anaemia, mitral and aortic disease, but no nodules. The temperature was only just above normal. Whilst under my care there was slight epistaxis, and later pleuro-pericarditis. The child died in February, 1901, of heart disease. A post-mortem examination was refused.

Summary: Sore throat; morbus cordis; anaemia; epistaxis; arthritis; death, after pleuro-pericarditis.

Case 6.—Jan., 1901. W. G., male, aged $2\frac{1}{2}$ years. This child had already been ill for seven months. The onset had been with pains in the joints and swelling of the knees and ankles. The doctor in attendance had called it rheumatic fever. When I saw the child he was suffering from severe mitral disease, with both dilatation and hypertrophy. His brother, whom I also saw in his illness, was suffering from unequivocal rheumatism. These patients were only brought for an opinion, and were not seen again, but the child was undoubtedly damaged for life.

Summary: Arthritis; morbus cordis; outlook bad.

Case 7.—March, 1901. E. H., female, aged $4\frac{1}{2}$ years. This was a very instructive example of the danger of rheumatism. Three months before, without a single definite symptom, she was noticed to be getting pale and progressively feebler. The first distinct warning was the occurrence of slight choreic twitchings. When first under observation there was striking muscular feebleness. The heart was feeble and dilated and the sounds faint. Soft pericardial friction was audible. No nodules were present. Fourteen days later thrombosis occurred in the left jugular, and the child died on March 23. The post-mortem examination showed pericarditis, multiple endocarditis, pleurisy, and broncho-pneumonia.

Summary: Anaemia; broncho-pneumonia; carditis; chorea; pleurisy; venous thrombosis; death; post-mortem examination.

Case 8.—August, 1901. J. O., male, aged $4\frac{8}{12}$ years. Came under observation for arthritis. His mother had suffered from rheumatic fever. His first attack of arthritis was in January, 1901, affecting the ankles and feet. This attack was followed by another in March, and a third in May. The fourth attack, in August, involved the metacarpo- and metatarso-phalangeal joints and both knees. There was irregular fever, with enlargement of the glands in the axillae and groins. The splenic dullness was also increased. Later, more of the smaller joints were involved, and the neck and back became stiff. The heart was dilated, but there was no murmur. This case went from bad to worse, and extreme emaciation was a prominent feature. Eventually the parents took him from me in disgust. A year later I inquired, expecting to hear that the child had died. The parents informed me that after four months in bed, and treatment by cod liver oil, he improved, and was now able to go to school. Later they brought him

to see me, and I found the enlarged glands were now normal, as also the splenic dullness. The cervical spine was rigid and flexed, and there was considerable periarticular thickening round the wrists. Both knee joints were enlarged and creaked on movement. More remarkable still was obvious heart disease. A loud mitral systolic murmur was audible, and the left ventricle was hypertrophied and dilated. In 1902 there was another attack of arthritis. In March, 1903, he was again brought to me very ill. His head was bent almost on to his chest, and his neck was swollen and stiff. The wrists, knees, and fingers were greatly swollen, and his arms terribly wasted. His heart was greatly enlarged, the liver reached the umbilicus, and there was ascites. In December, 1903, he was still living, but later inquiries failed to bring any reply, and there is little doubt that he must have died. This was a most unusual case, and possibly not rheumatic. In some respects it resembled Still's syndrome, and in others 'rheumatoid arthritis'. There was, nevertheless, no scientific objection to the explanation of all the symptoms as those of intractable rheumatism. Such a case has clearly strong bearing upon the whole problem of the relation of rheumatism to rheumatoid arthritis.

Summary: Repeated arthritis periarticular in type; heart disease; emaciation; enlarged glands and spleen.

Case 9.—June, 1901. Male, aged $4\frac{11}{12}$ years. The illness had commenced a week before with tired feelings and pain in the limbs, followed by diarrhoea and sickness. There was a history of rheumatic fever in the father's family. He was very ill and pale. His throat was reddened, and there was arthritis of both knees. The heart was dilated, and a systolic mitral murmur was audible, and was conducted into the left axilla. Five days later he developed acute pericarditis and pneumonia and died in three days. The post-mortem showed arthritis, early pericarditis, mitral endocarditis, a large spleen, and broncho-pneumonia. The diplococcus was isolated from the pericardial, cerebro-spinal, pleural, and arthritic exudations. This case died in three weeks.

Summary: Sore throat; anaemia; carditis; arthritis; broncho-pneumonia; death.

Case 10.—Oct., 1901. H. C., female, aged $4\frac{10}{12}$ years. Fourteen days before she had a sore throat, followed by multiple arthritis and heart disease. This child died in December of heart disease.

Summary: Sore throat; carditis; arthritis; death.

Case 11.—Dec., 1901. G. P., male, aged 4 years. The mother had rheumatic fever. The child was brought for heart disease. There was advanced mitral disease, and none of the ordinary evidences of congenital heart disease; on the other hand I could find no other proof of rheumatism. This case was lost sight of.

Summary: Heart disease.

Case 12.—Jan., 1902. A. H., female, aged 10 months. The father had rheumatic fever. At eight months she developed chorea. When seen, she had general chorea of moderate severity. The heart was dilated, and there was

a soft systolic mitral murmur. This case ran a favourable course. The chorea disappeared in four weeks, and the dilatation of the heart recovered, the murmur disappearing. At no time was there arthritis.

Summary: Chorea; cardiac dilatation; recovery.

Case 13.—Feb., 1902. G. S., female, aged $4\frac{7}{12}$ years. Four months before coming under observation she had suffered from multiple arthritis, and an illness which the doctor in attendance called rheumatic fever. The arthritis subsided in all joints but the knees, which remained obstinate and full of fluid. Her heart was dilated, and the first sound short and feeble. Energetic treatment with salicylates had failed and contractures were commencing. On stopping all salicylates, feeding abundantly and giving quinine, there was steady improvement. The irregular fever present subsided, and in three months there was complete recovery. During this period a small firm nodule appeared on the lower end of the left radius. In June, 1902, there was slight chorea. In September another nodule appeared at the lower end of the left radius. In January, 1903, further nodules of the same firm, indolent character appeared over the right carpus. In January, 1903, they had all disappeared, and there was apparently complete recovery. There were several unusual features about this case, and in particular the failure of the knee-joints to respond to vigorous salicylate treatment. Some will maintain that this is a proof that the condition was not rheumatic, a view I cannot accept, believing the specific action of the salicylates to be greatly overrated, and holding that the occurrence of chorea is a more trustworthy test of rheumatism. The nodules resembled those that are sometimes met with in the rheumatoid arthritis of adults. This case is again of particular interest as bearing upon our conception of rheumatoid arthritis. Some, in fact, most authorities, draw a rigid line between rheumatism and rheumatoid arthritis, an attitude which I venture to think is not supported either by scientific investigation or by clinical experience.

Summary: Multiple arthritis; cardiac dilatation; nodules; chorea; recovery.

Case 14.—March, 1902. P. C., female, aged 5 years. After two weeks of pains in the limbs, she came under observation with arthritis of both knee-joints and rheumatic broncho-pneumonia. Her heart was damaged; there were dilatation, early mitral endocarditis and pericarditis. She recovered with mitral disease after a long illness. In 1904 there was another attack of rheumatism. This child is still under my care.

Summary: Heart disease; arthritis.

Case 15.—June, 1902. A. T., female, aged 2 years. The father and a maternal uncle had had rheumatic fever, the latter dying of the disease. The child had been ill for three months with arthritis and heart disease. There was advanced heart disease, and a nodule was present on the right olecranon process. This child had a very severe illness, but ultimately recovered with a damaged heart, only to relapse in the following August.

Summary: Carditis; arthritis; nodules; lost sight of.

Case 16.—Oct., 1902. B. J., male, aged $4\frac{1}{2}$ years. This child, living in a damp house, was brought for chorea and early mitral endocarditis. He recovered with a mitral lesion.

Summary: Chorea; morbus cordis; recovery.

Case 17.—Jan., 1903. W. R., female, aged $4\frac{9}{12}$ years. The mother had had three attacks of rheumatic fever and her heart was damaged. Three weeks previously the patient had a sore throat followed by fever and pains in the limbs. The knees and elbows were swollen and stiff. The heart was not certainly damaged. Recovery followed the use of salicylates.

Summary: Sore throat; arthritis; recovery.

Case 18.—May, 1903. F. C., male, aged $3\frac{3}{12}$ years. She had chorea, followed by heart disease, the illness commencing fourteen days before coming under observation. There were relapses in October, 1904, and May, 1905. The heart showed permanent mitral damage.

Summary: Chorea; heart disease; partial recovery.

Case 19.—May, 1903. F. H., male, aged 4 years. The father had had rheumatic fever twice. There was a history of arthritis at three years. The recent illness had lasted three months. There were arthritis, profound anaemia, carditis, and nodules. Death occurred in June from haemorrhagic pericarditis. The diplococcus was isolated from the pericardial exudation.

Summary: Arthritis; carditis; nodules; anaemia; death.

Case 20.—June, 1903. E. C., female, aged $4\frac{6}{12}$ years. She had chorea at 3, arthritis at $3\frac{1}{2}$. She came under observation for active mitral endocarditis. The temperature was raised. This patient made a slow recovery with a mitral lesion.

Summary: Acute endocarditis; previous history of chorea and arthritis; recovery.

Case 21.—June 1903. H. T., female, aged $3\frac{11}{12}$ years. Four weeks previously there had been multiple arthritis, and this was followed by severe carditis and chorea. This case made a slow and incomplete recovery.

Summary: Arthritis; carditis; chorea; partial recovery.

Case 22.—June, 1903. P. C., male, aged $4\frac{10}{12}$ years. At $3\frac{10}{12}$ years there had been a previous attack of rheumatic fever. The present illness commenced with multiple arthritis, and was followed by severe carditis, which proved fatal at the end of June. The necropsy showed adherent pericardium, mitral tricuspid and aortic endocarditis.

Summary: Arthritis; carditis; death.

Case 23.—Nov., 1903. H. S., male, aged 5 years. One sister had suffered from rheumatic fever. The patient had been ill a year, first with sore throat, then with pains in the limbs, anaemia, and shortness of breath. These latter symptoms were present when first she came under observation. Recovery followed with an organic mitral lesion.

Summary: Anaemia; heart disease; partial recovery.

Case 24.—Feb., 1904. A. B., male, aged $2\frac{6}{12}$ years. His sister was under my care with rheumatism. The child himself was brought for pains in the

limbs and night terrors. There was no definite heart disease. This case made a good recovery.

Summary: Night terrors; arthritic pains; recovery.

Case 25.—May, 1904. E. W., male, aged $3\frac{9}{12}$ years. When $3\frac{4}{12}$ years he had an attack of multiple arthritis. This was a very fine boy, the son of a fireman, and in this the second attack his heart was greatly damaged. The parents lived at the fire-station, the ground floor of which was always wet and damp. The boy had further attacks in 1905, 1906, and 1907. A prominent feature was the repeated appearance of a rheumatic erythema. He is still under observation, with a greatly damaged heart.

Summary: Arthritis; erythema; carditis; anaemia; very partial recovery.

Case 26.—Feb., 1904. H. M., male, aged $4\frac{3}{12}$ years. He had had chorea for some weeks, and there was a history of a previous attack a year before. This patient had general chorea and cardiac dilatation. He made a good recovery.

Summary: Chorea; cardiac dilatation; recovery.

Case 27.—May, 1904. D. J., female, aged $3\frac{10}{12}$ years. The illness commenced with a slight sore throat, followed by irregular fever, multiple arthritis, anaemia, and carditis. Death occurred in August.

Summary: Sore throat; carditis; arthritis; anaemia; result, death.

Case 28.—August, 1904 G. O., male, aged $4\frac{6}{12}$ years. The father had had rheumatic fever. The onset of the illness was gradual with pains in the chest, breathlessness, and syncopal attacks. The heart was enormous, and there was a loud mitral murmur.

Summary: Carditis; lost sight of.

Case 29.—August, 1904. G. S., female, aged $4\frac{10}{12}$ years. She was said to have had rheumatism at $2\frac{4}{12}$ years. The mother had rheumatism, the father rheumatic gout. One brother had rheumatic fever three times. One sister had muscular rheumatism. The patient was brought very ill with arthritis, carditis and anaemia, nodules and chorea. He made a very imperfect recovery.

Summary: arthritis; carditis; anaemia; chorea; nodules; result, partial recovery.

Case 30.—Jan., 1905. R. B., female, aged $2\frac{9}{12}$ years. A history of seven days 'cold', followed by chorea was given. The movements were general and curiously jerking and extensive, with marked facial involvement. The heart was dilated, and there was a loud systolic mitral murmur. The child did well, but since that date has had several relapses, and at the present time (1907) there is definite mitral stenosis.

Summary: Chorea; morbus cordis; recovery with mitral stenosis.

Case 31.—Jan., 1905. W. C., male, aged $4\frac{3}{12}$ years. His illness had commenced some months previously with 'a sprained ankle and wrist'. For two months there had been chorea, and there was also definite cardiac dilatation and mitral disease. Recovery was uneventful, but with an organic mitral lesion.

Summary: Arthritis; chorea; heart disease; recovery.

Case 32.—Sept., 1904. A. C., female, aged 4 years. A brother was under my care with rheumatic fever. Three weeks' history of arthritis, anaemia, and shortness of breath was given. There was cardiac dilatation with mitral disease. Recovery followed with repeated relapses up to the present date (1907). There was organic mitral disease.

Summary: Arthritis; anaemia; cardiac disease; imperfect recovery.

Case 33.—Sept., 1904. W. S., female, aged $4\frac{1}{12}$ years. She had chorea for ten days. There was no obvious cardiac disease. Recovery followed.

Summary: Chorea; recovery.

Case 34.—Dec., 1904. L. T., male, aged 4 years. There was ten days' history of aching pains in the legs and refusal to walk. Fainting attacks were present. There was fever and the heart was dilated. Later a mitral lesion developed. Recovery, with organic heart disease followed.

Summary: Arthritic pains; morbus cordis; recovery.

Case 35.—March, 1905. R. W., female, aged $4\frac{6}{12}$ years. Six weeks previously she had had a sore throat, followed by multiple arthritis, nodules, and carditis. Death occurred in April, when, in addition, mediastinitis, perihepatitis, and perisplenitis were found to be present.

Summary: Sore throat; carditis; arthritis; mediastinitis; nodules; perisplenitis; perihepatitis; result, death.

Case 36.—May, 1905. E. N., female, aged $3\frac{6}{12}$ years. The father had had rheumatic fever. A paternal aunt had had fatal rheumatic fever. Four weeks previously, after some days of malaise, with pains in the feet and many other joints, definite arthritis developed in the hands and ankles. There was much sour perspiration. Later, pericarditis, endocarditis, arthritis, nodules, and anaemia were present, and death occurred early in June. There was no post-mortem examination.

Summary: Pericarditis; endocarditis; arthritis; anaemia; nodules; sweating; result, death.

Case 37.—Sept., 1905. M. A., female, aged 4. A three-weeks history of chorea was followed by mitral heart disease.

Summary: Chorea; heart disease; recovery.

Case 38.—Nov., 1905. B. S., female, aged $4\frac{11}{12}$ years. The parents had just gone into a new house. Fourteen days previously she had complained of pain in the head and 'aches' in the limbs, together with a sore throat. Three days later chorea commenced. There were in addition mitral disease, fever, and cardiac dilatation. After a long illness she recovered with a much damaged heart.

Summary: Sore throat; arthritis; chorea; heart disease; partial recovery.

Case 39.—Jan., 1906. W. C., male, aged $4\frac{3}{12}$ years. Three months previously he had suffered from 'a sprained wrist and ankle'. A month later chorea developed, hemiplegic in type with aphasia. There was slight dilatation of the heart; a good recovery followed.

Summary: Arthritis; chorea; cardiac dilatation; good recovery.

Case 40.—Feb., 1906. H. F., male, aged $1\frac{10}{12}$ years. This was not a clear case, but very suggestive. His father had suffered from rheumatic fever. The child, a weakly infant, had suffered for two months from swelling of the hands. His heart was greatly damaged, with all the characters of a mitral lesion, viz. mitral regurgitation, with much hypertrophy and dilatation. There was no cyanosis or clubbing. He was lost sight of.

Summary: Arthritis; heart disease.

Case 41.—June, 1906. C. K., female, $1\frac{1}{2}$ years. A brother was under me with active cardiac rheumatism. The child was taken suddenly ill with fever and a stiff neck, but there was neither arthritis nor heart disease. Recovery under salicylate treatment in seven days.

Summary: Stiff-neck; fever; recovery.

Case 42.—Sept., 1906. S. P., female, aged 3 years. The illness began suddenly with multiple arthritis, high fever, and much sweating. The heart was dilated. A good recovery followed under salicylate treatment.

Summary: Arthritis; cardiac dilatation; fever; sweating; recovery.

Case 43.—Sept., 1906. M. W., female, aged $4\frac{5}{12}$ years. Fourteen days before coming under observation she had a sore throat, followed by multiple arthritis, general pericarditis and mitral disease, anaemia, and wasting. Slow and imperfect recovery followed.

Summary: Sore throat; arthritis; carditis; anaemia; imperfect recovery.

Case 44.—Sept., 1906. E. E., female, aged $4\frac{10}{12}$ years. The mother had had rheumatic fever twice. This child had, eight months previously, suffered from an attack of rheumatic fever. The second illness had commenced three weeks before with slight pain in the chest, but no dyspnoea. There was general pericarditis. This case made an excellent recovery, with a slight mitral lesion.

Summary: Carditis; recovery.

Case 45.—Oct., 1906. W. B., female, aged $4\frac{3}{12}$ years. The family were living in a damp house in the north of London. The mother had suffered from 'gout', the father from 'rheumatic fever', and one sister, aged eight, from pains in the joints. The patient had been ailing for six months. There had been wasting, anaemia, and nocturnal pains in the joints. Her heart was much damaged, the mitral valve incompetent, and the cavities dilated. This case was lost sight of.

Summary: Anaemia; arthritis; wasting; endocarditis.

Case 46.—Nov., 1906. A. W., female, aged $4\frac{6}{12}$ years. She had had three days' illness with arthritis of the wrists and ankles. In addition, there was purpura over the buttocks, legs, and thighs, and the heart was dilated. Recovery occurred under treatment by rest and salicylates. She was not seen again.

Summary: Arthritis; purpura; cardiac dilatation.

Case 47.—Jan., 1907. H. D., female, aged 3 years. When $2\frac{1}{2}$ years this child had had an illness, in which the knees and ankles were swollen. Two months before coming under observation chorea had developed. The child was anaemic.

The heart was enlarged, and there was a double mitral murmur. She made a slow recovery, and in December, 1907, there was a slight relapse. Her father and paternal grandfather, and two paternal aunts, had suffered from rheumatic fever; her mother from rheumatism. The house was admittedly damp, with water in the cellars.

Summary: Chorea; anaemia; heart disease; partial recovery.

Case 48.—May, 1907. L. S., female, aged $3\frac{7}{12}$ years. Two weeks after tonsillotomy she complained of pains in the limbs, and became anaemic. When first seen there was a nodule over the occiput, and the heart was severely damaged. After treatment she recovered with a mitral lesion.

Summary: Anaemia; arthritis; morbus cordis; nodule; partial recovery.

Case 49.—Sept., 1907. F. A., female, aged $4\frac{6}{12}$ years. The family went into a damp house two months before and the father developed rheumatism in the joints. The patient complained of pains in the legs, arms, and abdomen. There was fever, and she had an excited action of the heart. Later, a mitral murmur developed.

Summary: Arthritic pains; fever; morbus cordis; partial recovery.

Case 50.—Nov., 1907. H. C., male, aged $4\frac{8}{12}$ years. She had chorea for a fortnight. The movements were general. Speech was considerably affected. The heart was rapid; the first sound at the apex was blurred; the temperature was raised. He is still under treatment.

Summary: Chorea; early heart disease; fever.

Case 51.—Dec., 1907. G. O., male, aged $4\frac{8}{12}$ years, subject to sore throats. The father has rheumatism. One sister had rheumatic fever. The patient four weeks before complained of pains in the left knee. Arthritis of both knees, fever, and dilatation of the heart were found. The urine contained albumin. He is still under observation.

Summary: Arthritis; fever; cardiac dilatation; albuminuria.

Case 52.—Dec., 1907. E. S., male, aged $4\frac{10}{12}$ years. The father and brother have rheumatism. Pains in ankles and knees for some weeks, followed by chorea of moderate severity were complained of. Now there was definite chorea and mitral heart disease. He is now under observation.

Summary: Arthritis; chorea; morbus cordis.

In this series the frequency of the association of rheumatism with damp houses is noteworthy, as also the strong family history of the disease in many instances.

Appendix II.

Seventeen cases of rheumatism in children over five years, in which there was a history of a previous attack before the fifth year.

1.—S. A., female, aged 6. Repeated attacks and severe cardiac damage. Arthritis at 15 months.

2.—F. P., male, aged 7. Chorea. Arthritis at $2\frac{1}{12}$ years.

3.—B. F., female, aged 10. Severe morbus cordis of old standing. Muscular rheumatism at $1\frac{6}{12}$ years.

4.—C. B., male, aged $5\frac{5}{12}$. Severe rheumatism and heart disease. Rheumatism at 3 years.

5.—S. B., female, aged 6. Purpura. Arthritis and dilated heart. Rheumatism at 3 years.

6.—L. D., male, aged 6. Rheumatic heart disease. Arthritis at 4 years.

7.—L. B., male, aged $5\frac{3}{12}$. Severe rheumatic heart disease. Rheumatism at $4\frac{6}{12}$ years.

8.—J. S., aged $6\frac{1}{12}$. Severe rheumatic heart disease. Rheumatic fever at 3 years.

9.—J. R., female, aged 6. Severe heart disease. Acute rheumatism between 4 and 5 years.

10.—H. K., male, aged $5\frac{10}{12}$. Fatal rheumatic fever. First attack at 4 years of age.

11.—J. B., male, aged 7. Morbus cordis. Rheumatism at 3 and 5 years.

12.—L. R., female, aged 6. Advanced heart disease. Arthritis at 15 months.

13.—E. P., female, aged 6. Chorea and heart disease. Chorea at 4 years.

14.—J. W., male, aged 11. Fatal rheumatic fever. Rheumatic fever at 3 years.

15.—F. W., female, aged $8\frac{1}{2}$. Rheumatic arthritis and heart disease. First attack at 4 years.

16.—C. C., male, aged 9. Rheumatic heart disease and nodules. Articular rheumatism between 4 and 5 years.

17.—F. C., female, aged 8. Chorea and morbus cordis. Articular rheumatism at 4 years.

CHLOROMA AND ACUTE LYMPHATIC LEUKAEMIA, WITH AN ACCOUNT OF FOUR CASES, AND A DISCUSSION OF THE PATHOLOGY OF THE DISEASES

By C. H. TREADGOLD, M.A., B.C.

With Plate 33.

Owing to the comparatively scanty literature associated with chloroma and acute leukaemia, the detailed reports of the following cases are given, with the hope that they may add a little to the knowledge of diseases which are peculiarly interesting apart from their great rarity.

Case I.

Edward Plimmer, aged 41 years, was admitted to the London Hospital on April 20, 1907. He was a bootmaker, and had always been a teetotaller. He could remember no previous illness of any severity. He was married, and had three healthy children.

The patient had been ill for three weeks. His first trouble was exhaustion on walking. A fortnight ago he injured his right arm, and the bruise extended to the hand. The next day purple patches appeared on the chest and arms. About the same time the gums started to bleed, and this had been getting worse. On the morning of the 20th he had a tooth extracted, and as the bleeding could not be stopped, he came to the hospital. Whilst waiting in the 'receiving-room' he fainted, and was admitted as an in-patient. The temperature on admission was 99°.

April 21. The patient was very anaemic. There was a purpuric eruption on the arms, legs, and upper part of chest; also purple spots on the inside of both cheeks. The arms below the elbows were swollen, and painful. The glands were slightly enlarged in the posterior triangles of the neck, axillae, and groins.

An examination of the heart and lungs showed nothing abnormal except a bruit at the base of the heart, which was probably exocardial or haemic.

The breath was very offensive, and had been so for fourteen days, but the tongue was clean, and there was no marked stomatitis. The tooth socket was

plugged, but still oozed. The abdominal organs appeared normal, with the exception of the spleen, which could just be felt. An examination of the eyes showed the fundi were pale; the right fundus had two small punctate haemorrhages near the disk. The edge of the left disk was blurred, and there were punctate haemorrhages in and around it. The knee-jerks were present. The urine was amber-coloured, acid, sp. gr. 1,022, and contained no albumin.

April 25. The gums were still oozing. Melaena since the 23rd.

Blood count.	Reds	3,200,000 per c. mm.
	Whites	240,000 „
Differential count.	Large mononuclear cells	52%
	Lymphocytes	21%
	Polymorphs	27%

April 26. The patient was collapsed. The oozing from the gums and the melaena continued. The purpuric spots became fainter. The temperature varied from 100° to 104°. The patient died in the evening.

Post-mortem. The body weighed 8 st. 5 lb., and was 6 ft. 2 in. in length. On the neck, chest, arms, and legs were very small purpuric spots. There were a few on the back. On the abdomen the spots were faded, and of a yellowish-brown colour. Beneath the right eye, and over the right upper limb, were diffuse yellow stains, and over the right shin was a purple bruise. The lips were very pale. The gums of the upper jaw were thickened, spongy, and foul.

The thymus weighed ½ oz. The cut surface was oedematous, yellow, and fatty. The pericardium contained 1½ oz. of straw-coloured fluid. The surfaces were smooth and glistening. The heart weighed 11½ oz. The surface was covered with ecchymoses. The right side of the heart was filled with a green, gelatinous, elastic, post-mortem clot. A similar clot filled the pulmonary artery. The left side contained a similar but smaller clot. The valves were healthy, except for four small, yellow patches on aortic cusp. There were a few sub-endocardial ecchymoses.

Glands. The submaxillary were discrete, and up to the size of a hazel-nut. The cut surface was slightly swelled, green, and moist with small, haemorrhagic spots. The glands of the posterior triangles were also discrete, but smaller. The cut surface was a greenish grey, flecked with red. The largest of the deep cervical glands were the size of a thrush's egg, the cut surface was green, and flecked with red and pink. The lower cervical were the size of two peas. The cut surface was greenish, with some anthracosis. The axillary glands were larger on the right side—the largest being 2 by 3 cm. The cut surface of some showed a slight greenish tinge. The tonsils were enlarged, the surface was haemorrhagic; the cut surface was green, alternating with haemorrhages. The lingual tonsil was swollen, and nodular; the surface haemorrhagic, the cut surface green.

Pharynx. There were greenish nodules in the submucosa.

On opening the chest the pleural cavities contained a minute quantity of clear blood-stained fluid; the pleural surfaces were smooth and glistening; there were no adhesions.

Lungs. The right lower lobe was oedematous, and on pressing, an abundant, brown, frothy fluid exuded; on the surface were one or two haemorrhages; otherwise, the lungs were normal.

Abdomen. The peritoneum was smooth and glistening; there were haemorrhages on the surface of the descending colon. The spleen weighed 12 oz. It was large and flabby. The cut surface was brownish-pink, while the smooth trabeculae and the small Malpighian corpuscles were indistinctly visible. Green, gelatinous clots were seen in some of the vessels. The cut surface of the mesenteric glands had a greenish tinge. The liver weighed 4 lb. 9 oz. It was somewhat enlarged, and there was one small haemorrhagic area over the left lobe; the cut surface was smooth, and brown, with a well-marked pattern. Of the gastro-hepatic glands some showed greenish spots. Both kidneys together weighed 12 oz. The capsule of the left was thin, but stripped fairly readily. The medulla was two-and-a-half times the width of the cortex; it was pink, and sharply demarcated from the cortex, which was pale grey with occasional traces of straight pattern. The right was similar. The bladder showed numerous small haemorrhages into mucous membrane.

The inguinal glands were larger on the right side. The largest was $\frac{3}{4}$ by $\frac{1}{2}$ inch. The cut surface was yellowish brown.

Intestines. Peyer's patches and some of the solitary follicles were atrophic. In the transverse colon and rectum were several large irregularly raised areas covered with greenish sloughs.

The skull cap was very thin, and showed a little pink diploe. The dura mater stripped readily. There was greenish post-mortem clot in the superior longitudinal and lateral sinuses. The brain was anaemic and oedematous. The pituitary and pineal bodies showed nothing remarkable.

Bones. The marrow of the sternum, inner end of right clavicle, lumbar vertebrae, ribs, and the left angle of jaw was of a pinkish grey. As regards the right femur, in the upper part the marrow was soft and of a pinkish grey; the centre of the shaft was deep red with soft greyish nodules, while in the lower half the marrow was yellow, with deep red areas.

A few of the chief points gleaned from a microscopical examination of the affected tissues may be summarized as follows:—

In all organs examined, there were multiple small haemorrhages. There was marked degeneration of the small blood-vessels; also well-marked infiltration of their walls by the white cells of the blood. The cells forming the infiltrations (allowing for differences produced by hardening the sections) corresponded to the white cells of the blood. The smears made from the different organs—marrow, tonsil, and axillary gland—showed cells, chiefly of the large mononuclear type, a few with definite, others with indefinite, granulation, chiefly

neutrophile; but the majority were without granulation. However, the smears were not very successful.[1]

Sections made from hardened pieces of the affected tissue showed large mononuclear cells which roughly conformed to two types; in future, such cells are referred to as belonging to type 1 or type 2, respectively. The distinction drawn between these two types may not seem very clear, but it was fairly evident microscopically.

Type 1. Cells with large, lightly staining nuclei, containing a variable, though usually small, amount of chromatin. Some have much protoplasm, others little.

Type 2. Cells with very large, light, vesicular, and feebly reticulated nuclei; often there was an appearance of a nucleolus. As a rule, there was little protoplasm, sometimes a fair amount. These seemed to be degenerated forms.

Sections of the marrow showed cells similar to those in the blood and tissues. There were scanty remnants of the germinal centres in the angular gland and in one from the posterior triangle. There was infiltration of the periglandular connective tissue and also marked endothelioid proliferation. The germinal centres were better shown in the axillary, and better still in the inguinal glands. Intercellular substance and cells with large nuclei and abundant fused protoplasm were much better shown in the cervical glands; they were more marked still in the buccal and pharyngeal lymphoid tissue, i.e. in the green lesions; much less noticeable in the axillary, and hardly at all in the inguinal glands.

The origin of the cells in glands and infiltrations. Cells of type 2 undoubtedly came from the blood. The proof of this is, first, that similar cells were seen in sections through blood-clot and marrow; secondly, that small haemorrhagic extravasations were usually present in their vicinity. The majority of cells conforming to type 1 probably came from the blood also: first, because many were present in sections through blood-clot and marrow; and secondly, in the various organs these cells were seen infiltrating the walls of the smaller blood-vessels. However, many of them had more protoplasm than was consistent with the cells seen in the blood. (This has been described by other observers.) It was especially noticeable in the cervical glands and buccal

[1] The terms used to describe the various cells seen in the films and smears of these cases, may here be defined:—

By a lymphocyte is understood a cell about the size of or rather smaller than a red blood corpuscle, containing a deeply staining nucleus and a small rim of basophile protoplasm. A cell similar to but somewhat larger than this, and often with a more lightly staining nucleus, is referred to as a large lymphocyte. Cells with reniform nuclei are differentiated from the transitionals. The non-granular undifferentiated cells which remain are referred to in general as mononuclear or large mononuclear cells, and this term is qualified when necessary. These cells are sometimes referred to as marrow lymphocytes or undifferentiated marrow cells. When either of these expressions is made use of, they must be taken to be identical with the large mononuclears previously defined.

lymphoid tissue. Possibly increased protoplasm was a sign of degeneration, as this increase was accompanied by an excessive amount of intercellular substance. Probably some of these cells were abnormal types of endothelioid cells. Similar ones occur in lymphoid tissue in certain of the specific fevers. However, intermediate types were not well marked. The spleen gave one the impression of being infiltrated with cells from without. The presence of granulated cells in the smears confirmed the impression already gained from the blood and marrow, namely, that many of these cells were atypical myelocytes.

Microscopical appearances. The films and smears in these four cases were stained with Leishman and Jenner's stain; the hardened sections were treated with haematein and eosin.

Blood count.	Reds	3,200,000 per c. mm.
	Whites	240,000 „
Differential count.	Large mononuclear cells	56%
	Small (resembling lymphocytes)	7%
	Degenerated forms	5%
	Polymorphs (including transitionals)	28%
	Mononuclears with reniform nuclei	2·5%
	Neutrophile myelocytes	1·5%

The large mononuclears varied up to four and a half times the size of a red blood corpuscle; the majority were from two-and-a-half to three times the size. The nucleus was round, stained blue, and looked markedly granular. As a rule, it showed large, pale vacuoles. Often no protoplasm could be made out, but usually a basophile rim of protoplasm was visible in the larger cells; this generally contained dark, basophile granules (the so-called azur granules).

Some of these cells possessed acidophile protoplasm and rarely a few neutrophile granules; apart from these granules they were indistinguishable from the large mononuclears. There were no other distinguishing features between large and small forms. Some mononuclears (both large and small) showed small knob-like processes projecting from their protoplasm. A few large cells with reniform nuclei and hyaline protoplasm were also seen. Many cells appeared to be dividing, apparently by direct division.

The polymorphs and transitionals were highly abnormal. They varied from one to four times the size of a red blood corpuscle. In many, the protoplasm contained no granules while remaining faintly acidophile. Sometimes it contained both neutrophile and basophile granules. The nuclei showed a marked appearance of basophilic granulation and were usually vacuolated. In the large forms the nuclei were often large and swollen, making it difficult to distinguish the cells from the large mononuclears with faintly acidophile protoplasm.

Sections of white marrow showed some fat globules, lymphocytes, both large and small, many cells of types 1 and 2, cells with reniform nuclei, polymorphs, and many degenerated red blood corpuscles. The cells of type 2

possessed rather more protoplasm than those seen in sections through blood-clot.

Sections through red marrow showed more red corpuscles, whilst many of the white cells had more protoplasm and an indefinite appearance of granulation; there were also more polymorphs. Smears of the white marrow showed cells with granular vacuolated nuclei and a varying amount of (?) non-granular protoplasm; they went up to four times the size of a red blood corpuscle. There were few definitely granular cells. Some dark lymphocytes, about the size of a red blood corpuscle, were also seen. The red marrow showed many cells containing small neutrophile granules and a high percentage of abnormal-looking transitionals and polymorphs. Sections through blood-clot showed many cells of type 2, more of type 1, many polymorphs, a few (?) endothelioid cells and much transparent fibrin. Granular cells could not be differentiated. The cells looked considerably smaller than those in the films. The process of hardening causes the cells to shrink considerably since the red corpuscles also look smaller. On the other hand, preparing blood-films probably makes many of the white cells look larger.

Angular gland. The capsule and trabeculae were badly marked and infiltrated with cells of type 1, the majority of which possessed a fair amount of protoplasm. Few cortical centres and lymph sinuses were seen. These latter were lined by flattened cells with spindle-shaped nuclei. In the sinuses were endothelioid cells with small nuclei, similar cells with branching—sometimes stellate protoplasmic processes, cells of type 1, the majority with little protoplasm, also lymphocytes and a few cells conforming to type 2. In the scanty remnants of the germinal centres were lymphocytes; also large lymphocytes with lighter and more reticulated nuclei. In the vicinity was delicate intercellular substance, consisting of the protoplasmic processes of endothelioid cells, cells of type 1, and filaments which sometimes contained spindle-shaped nuclei. In the medullary part were many cells of type 1, some linked together by protoplasmic processes; a few conformed to type 2; also lymphocytes, both large and small. A few small polymorphs were present both in capsule and medulla.

Gland from posterior triangle. Multitudes of cells throughout section resembling lymphocytes and large lymphocytes were present. Many cells conformed to types 1 and 2, both in cortex and medulla. The cells of type 1 were usually in clumps and connected to one another by protoplasmic processes. Much inter-cellular material, but few filaments with spindle-shaped nuclei, were present. No lymph sinuses were seen. The cells infiltrating the capsule conformed to type 1. The connective tissue and periglandular fat was infiltrated to a slight extent. There were small, isolated collections of dark lymphocytes in the cortex. Many ordinary endothelioid cells were present throughout the section. One giant endothelioid cell was seen in the cortical part; this contained two white cells and some brown pigment, and was the only instance in which phagocytosis on the part of endothelioid cells was observed apart from the spleen. A section through the angular and neighbouring

submaxillary gland showed there was no general infiltration of the connective tissue.

Axillary gland. The capsule and periglandular fat were only slightly infiltrated. A good many cells of type 1 were present, but cells joined by their protoplasm were scarce, compared to the previous sections; the trabeculae were swollen and infiltrated in places with these cells—type 1. There were few cells corresponding to type 2, and less hyaline intercellular material. The deficit was made good by vast numbers of lymphocytes, both large and small, the germinal centres being a little better defined.

Inguinal gland. Much sclerosis was found both in cortex and medulla. The trabeculae were thickened, while the reticulum contained many large, pale, spindle-shaped nuclei, and was very dense. There were many distinct patches of small lymphocytes in the cortex; mingled with and surrounding these were cells corresponding to type 1, some with much, others with little, protoplasm. One mononuclear eosinophile was seen. A small haemorrhage into the pericapsular connective tissue showed many red corpuscles but very few white cells. However, a few cells of types 1 and 2 were seen in the surrounding areolar tissue, otherwise cells of type 2 were scarce; a few were seen in the lymph sinuses accompanied by red corpuscles and endothelioid cells.

Smears of an axillary gland showed a few cells with neutrophile and azur granulation.

Tonsil. A few lymphoid nodules were seen. The rest of the section consisted of cells of type 1, which were numerous and in many cases connected with each other and with abundant intercellular material by protoplasmic processes; there were also cells of type 2, and cells resembling lymphocytes; occasionally cells with reniform nuclei were also present. The pharyngeal and lingual tonsils showed a similar appearance. Smears from the tonsil showed cells with vesicular nuclei and little or no protoplasm. Thousands of diplococci were present. Smears from the cut surface showed cells resembling those seen in the blood. A few showed small neutrophile granules.

Spleen. There were many cells with large nuclei, some conforming to type 1 and a few to type 2. The residue seemed to be pulp cells, a few of which contained red blood corpuscles. They could not always be distinguished with certainty from cells of type 2. There seemed to be a greater proportion of cells with a fair amount of protoplasm and vesicular nuclei, which nuclei were rather smaller than the cells of type 2 as seen in other organs. There were a good many ordinary endothelioid cells, and one giant endothelioid cell was noticed. There were many red blood corpuscles scattered throughout the section. The blood-vessels were degenerated, especially the veins, and their coats were infiltrated with cells of type 1. Remnants of the Malpighian bodies were seen; they consisted of a degenerated arteriole surrounded by lymphocytes mingled with endothelioid cells.

Liver. The parenchymatous cells were in an advanced stage of cloudy swelling, and detached islands of these were seen all over the section, surrounded

by mononuclear cells. Glisson's capsule was infiltrated, whilst the intralobular veins had for the most part degenerated and disappeared, being replaced by masses of mononuclears lying between the liver-cells. The small branches of the hepatic artery were also infiltrated and degenerated. In detail, the infiltration consisted of cells of types 1 and 2, lymphocytes, and polymorphs.

Kidney. There was marked cloudy swelling and degeneration of the tubules, but the glomeruli were not much affected. Masses of mononuclear cells were seen in the cortex, especially just beneath the capsule, where they had infiltrated and replaced the kidney substance. Strings of these cells were seen in the medulla between the tubules; they had evidently reached it by growing down from the cortical masses in the inter-tubular connective tissue. The small veins had degenerated to a considerable extent, and, in places, mononuclears of type 1 could be seen passing through the vessel wall. Degenerative change was much less marked in the arteries. Lymphocytes and polymorphs were present, but few cells of type 2.

Case II.

Albert Miles, aged 3 years, was admitted to the London Hospital on April 4, 1906. He was a 'full time' child, and was breast fed up to fifteen months old. He was strong up to this illness. His mother was strong, and had three other children, all healthy. His father died of dropsy just before the patient's birth.

The child had been ill for four months, having been attended by a doctor at home. He first of all wasted considerably, and then lost the use of his legs; several weeks previous a lump appeared on the head, followed by one on the right cheek. These were followed by lumps on both sides of the neck, larger on the right side. He first started bleeding from the nose three weeks previous, and had been getting worse since. He had been suffering from pains in the legs, and had been sleeping badly.

On admission to Hospital he was very anaemic; his lips and conjunctivae were white, while the skin was of a peculiar colour—very pale and greenish yellow. The breath was foul. There was a hard lump on the upper part of the forehead over the right frontal bone; this was movable under the skin, and to some extent over the deeper structures. A similar swelling was seen over the right parotid gland. There was glandular enlargement at the angle of the lower jaw on the right side. Small, hard, freely movable glands could be felt in both submaxillary regions, axillae, and groins. The suboccipital glands were not palpable. The temperature was 104·6°. He had a slight cough; the respirations were 35 per minute. Stethoscopic examination revealed nothing abnormal. The pulse was 120; the area of cardiac dullness was normal; the heart-sounds clear. The patient's breath was very foul, and there was bleeding from the gums and lips. The liver was much enlarged; the spleen palpable, and firm, and the stools contained blood. Only a small quantity of urine

was passed; it contained blood, and a small amount of albumin. The blood itself was hydraemic, and pale; it flowed readily, and showed little tendency to clot.

Blood count.	Reds 1,800,000 per c. mm.	
	Whites 320,000 „	
Differential count.	Large mononuclear cells . . .	66·6 %
	Small mononuclear cells . . .	26 %
	Polymorphs	7 %
	Eosinophiles	·4 %

April 8. The patient complained of pain in the left forearm, which was found to be oedematous. The temperature was 104·8°; the pulse 120 per minute; the respirations 45. There was consolidation at base of left lung.

April 11. He was more wasted and anaemic; the swelling of the left forearm persisted.

April 12. The patient was more listless, and passed blood freely with the motions.

April 13. He was weaker, and delirious. The temperature was 101°; the respirations 45 per minute and sighing in character. The pulse was very feeble. Death occurred later in the day from haemorrhage and exhaustion.

Summary of post-mortem. The glands on the right side of the neck were much enlarged all the way up; the deep glands being chiefly affected. On section, a few small haemorrhages into the gland substance were noticed, while the cut surface was of a bright pea-green colour. The glands on the left side of the neck were smaller, but otherwise similar. The glands all over the body were in the same condition, but the green colour was not so vivid as in the cervical glands.

There were many sub-pericardial petechiae. The heart was pale, fatty, and bloodless. There was recent pleurisy over the lower lobe of the left lung, which was rather friable, and studded throughout with many white patches. On section these appeared raised, and were about the size of very small peas. The patches were strongly suggestive of lymphoid nodules. A little fluid blood exuded on squeezing, and the lung sank in water. The right lung, and upper lobe of left were healthy.

The spleen weighed 3½ oz. It was large and pale, but otherwise looked healthy. There were many retro-peritoneal haemorrhages. The cortex of the kidneys was very pale; the pyramids, dark red. The tissue round the pelvis was ploughed up with haemorrhages. The liver weighed 1 lb. 6 oz. It was pale. Glisson's capsule was well marked.

The brain was very anaemic. There were haemorrhages in the pia mater, and all over the cerebellum. The corpus callosum was full of haemorrhages. Punctiform haemorrhages were present throughout the brain substance and these were especially marked in the internal capsule.

There was a lump the size of a broad bean over the right frontal bone,

between the skin and the pericranium. On section it was purple. A similar lump was found in the parotid gland.

Microscopical examination. Blood count. Reds 1,800,000
Whites 320,000

Differential count with $\frac{1}{12}$ obj.

(1) Degenerated forms, chiefly large mononuclears	50·35 %
(2) Large mononuclear cells	17·85 %
(3) Ditto, but with reniform nuclei	3·21 %
(4) Forms intermediate in size between large and small	5·71 %
(5) Ditto, but with reniform nuclei	1·42 %
(6) Cells somewhat resembling large lymphocytes but showing degenerative changes	6·42 %
(7) Lymphocytes	1·78 %
(8) Polymorphs, including transitionals	6·42 %
(9) Cells resembling large mononuclears but with neutrophile granules in their protoplasm	6·42 %
(10) Eosinophile leucocytes	·35 %

The mononuclears showed a marked differentiation into large and small cells, of which the former greatly predominated. There were many degenerated forms and 'ghost cells', in fact the large mononuclears with few exceptions showed marked signs of degeneration. In all the large cells the nuclei looked granular and took the stain faintly. They were surrounded by a varying width of hyaline, but sometimes faintly granular protoplasm. These cells varied a good deal in shape and in many cases there appeared to be pseudopodial projections of the cell protoplasm. The nuclei were for the most part roughly circular in outline; a few were kidney-shaped. The large mononuclears were, on an average, three times the size of a red blood corpuscle; a few were five times the size. The large cells which contained a few small neutrophile granules, were otherwise identical with the large mononuclears. Many more large cells presented an appearance of neutrophilic granulation, but it was very difficult to make certain of this point. Many of the large mononuclears had an eccentric nucleus. In all probability many of them were akin to myelocytes. The intermediate forms were like the large, differing only in size.

In many cases the nucleus could not be differentiated from the protoplasm, the whole cell presenting a cloudy appearance. In the more degenerated forms the nuclei stained a mauve colour, while in the less degenerated the nuclei stained a light blue. In some cases the cell presented the appearance of a filmy sponge, in other cases it was a mere shadow. The polymorphs looked misty and otherwise normal. The majority were small, a few abnormally large—up to four times the size of a red blood corpuscle. The neutrophile granules did not show up well and the large forms often contained a few basophile granules. Their nuclei for the most part stained well, showing a reticulated

structure with thickening at the nodal points. Very few indications of proliferation were noticed. Very slight poikilocytosis was present. An occasional normoblast was seen. Probably the mononuclears looked so large because, being degenerated, they were more easily crushed in making the film. In all these cases it was impossible arbitrarily to distinguish small from large mononuclear cells. In distinguishing them, attention was paid to the depth of staining as well as to the size of the cell.

Lymphatic gland. The capsule was poorly marked. What remained of it was infiltrated by large mononuclear cells. The distinction between cortex and medulla was lost. However, there were a few small aggregations of lymphocytes in positions which corresponded to the germinal centres, but otherwise comparatively few cells resembling normal lymphocytes were seen. One or two small lymph sinuses were seen; they contained a few cells, chiefly large mononuclears. Trabeculae were present but looked swollen and degenerated; many of them were infiltrated with large mononuclear cells. Many of these had acidophile protoplasm, and some had an indefinite appearance of neutrophile granulation, though no definite granules could be made out. In the medulla these cells were arranged in small masses with clear spaces between. Many appeared to be dividing. The majority possessed a fair amount of protoplasm which in many cases was fused with that of adjoining cells. These cells had large nuclei, containing a variable amount of chromatin. The majority of nuclei were circular or oval; a good many were irregular or constricted; a very few were reniform. In a few cells two nuclei could be seen, in a very few three. A fair amount of intercellular substance, connected with the protoplasm of some of these cells, was present. A few cells corresponded to type 2, i.e. cells with very large and clear nuclei, containing little chromatin, but which sometimes appeared to contain a nucleolus. As a rule they possessed little protoplasm. A few polymorphs were noticed. Not many endothelioid cells, few cells resembling splenic pulp cells, a good many red blood corpuscles and a few small cholesterin crystals were also noticed.

Scalp tumour. This consisted of a localized subcutaneous infiltration which lacked a definite capsule. Strands of degenerated connective tissue were seen in the growth, also in places a delicate reticulum apparently derived from the connective tissue of the part. There were multiple haemorrhagic extravasations all over the section. A good many capillaries were noticed, many with stomata in their walls. There was degeneration of the small blood-vessels at the periphery; this was especially marked in the adventitia; in one case proliferation of the intina was seen. There was no definite evidence of new capillary formation, although the walls of some looked fairly healthy. The major portion of the tumour was made up of cells similar to those seen invading the vessel walls (i.e. type 1). These were arranged in a disorderly manner, some being in clumps, others isolated from each other, while the interstices were filled up chiefly with degenerated red blood corpuscles. As a rule, the mono-

nuclears possessed a good deal of protoplasm, and in places cells appeared to have fused together. One giant cell was noticed. It consisted of a large mass of blurred protoplasm, containing six large nuclei. Many dividing forms were seen, but few cells corresponding to type 2 were noticed. Few cells resembling lymphocytes and endothelioid cells. A few polymorphs were present. As a result of the microscopical examination one would have expected the tumour to have shown a greenish colour. However, the quantity of extravasated blood was so great as completely to obscure this change, supposing it to have been present.

Liver. The liver cells were in an advanced stage of cloudy swelling. Mononuclears, similar to those described in other organs, were seen throughout the section, but were particularly dense in the region of Glisson's capsule, where they surrounded the vessels and bile ducts. The walls of the blood-vessels were infiltrated and in some instances had ruptured. The veins were especially involved, but the small bile ducts were intact. Many detached islands of liver cells were seen, surrounded by mononuclear cells.

Lung. The alveoli were filled with exudate, while the intra-alveolar capillaries were distended with white cells. There were multiple haemorrhages everywhere. The intra-alveolar tissue was diffusely infiltrated with cells similar to those in the other organs examined—perhaps there were more cells resembling those of type 2.

Heart. The connective tissue between the muscle fibres was infiltrated by a few mononuclear cells.

Case III.

Annie Banks, aged 39 years, single, was admitted to the London Hospital on June 10, 1906. There was no history of illness, except scarlet fever when a child. Her father and mother were living, the former aged 85, and the latter 78. She had two brothers, both living and healthy.

The present illness commenced two months ago with influenza; since then she had had bad headaches, and day by day noticed herself getting paler and weaker. On June 5 she fainted. On June 7 purple patches appeared on the skin; since then fresh spots had appeared daily. On June 9 she passed dark stools and vomited persistently.

On admission to the hospital she was very anaemic; her hands, feet, and conjunctivae were white and bloodless. Her colour was extraordinary and suggested pernicious anaemia. Her temperature was 102°, and she was very drowsy. On the arms, legs, and abdomen were purpuric patches, as well as haemorrhagic spots. The glands in the neck, axillae, and groins were palpable and freely movable, but not abnormally enlarged.

An examination of the respiratory and circulatory systems revealed nothing of importance. The tongue was dirty, and the breath foul. There had been no nausea since admission. Neither the liver nor the spleen were palpable, but

the splenic dullness was increased. The urine was amber-coloured, acid, sp. gr. 1,018, and contained no albumin.

The patient complained of severe headache, indistinct vision, and slight difficulty with her speech. There was no paralysis or wasting of isolated muscular groups, and the pupils were equal, and reacted to light and accommodation.

June 12. She was worse, and more drowsy. The temperature was 104°.

Blood count. Reds 1,400,000
Whites 50,000

Differential count.

Large mononuclear cells	84·4%
Lymphocytes	14%
Polymorphs	1·6%

June 15. The patient was worse. The temperature had been coming down, and was now 97·8°. The glands in the neck and axillae were very slightly enlarged. There had been no further haemorrhages.

Blood count. Reds 700,000 per c. mm.
Whites 121,000 „

Differential count.

Large mononuclear cells	87·8%
Lymphocytes	10·6%
Polymorphs	1·6%

June 16. The patient was semi-conscious; the pulse was very weak and rapid; the temperature 97·6°. The liver and spleen could not be felt. There had been no further haemorrhages.

June 18. The patient was absolutely unconscious. There were fresh purpuric spots. The respirations were 64 per minute and stertorous in character. The temperature rose suddenly to 105°. The pulse was 120, and very weak.

Blood count. Reds 646,000
Whites 180,000

The films now showed a few normoblasts.

Differential count.

Large mononuclear cells	93·2%
Lymphocytes	6·8%
Polymorphs	·8%

The patient died later in the day from asthenia. The rapidly progressive anaemia, accompanied by a simultaneous increase in the white cells, more especially of the large mononuclears, were points worthy of notice.

Post-mortem.

External Appearances. The body seemed rather wasted. There were many cutaneous haemorrhages; these were particularly large on the outer side of the right thigh and arm; also over the left hand and buttock.

Both pleurae were quite healthy and free from adhesions. The bronchial

glands were not enlarged. The lungs were a little oedematous, the right lower lobe being in a condition of solid oedema; otherwise there was no change. The larynx was healthy.

The visceral layer of the pericardium showed numerous petechiae. The heart weighed 10 oz. There were many subendocardial petechiae. The right side was filled with large, soft, pale clot; pale clot was also found in the left ventricle. The muscle showed marked tabby-cat striation. The vessels were healthy.

Abdomen. A few, small, subperitoneal haemorrhages were present on the bowel. The mesenteric glands were smaller than usual. The spleen weighed 8 oz. It was bound down by some adhesions to the diaphragm. On section, no Malpighian tufts were visible. The substance was firm and somewhat pale, but otherwise looked healthy. The kidneys together weighed 10½ oz. Their substance was very pale, and the capsule did not strip readily. Numerous isolated petechiae were present in the mucous membrane of the stomach. The liver weighed 3 lb. 6 oz. The organ looked healthy and Glisson's capsule was not visible.

Brain. There were numerous haemorrhages in the meninges; also many minute haemorrhagic extravasations in the brain substance of the right occipital and one large one in the substance of the pons.

The marrow of the sternum was a pale grey.

Microscopical examination. Blood. Differential count with $\frac{1}{12}$ obj. from films made June 15, 1906.

Large mononuclear cells	62·75 %
Ditto, with reniform nucleus	4·5 %
Intermediate between large and small	9·0 %
Ditto, with reniform nucleus	·75 %
Cells the size of normal lymphocytes	6·0 %
Polymorphs	1·5 %
Myelocytes (neutrophile)	·25 %
Eosinophile leucocytes	·25 %
Free nuclei	2·25 %
Degenerated forms	13·5 %

The films showed a great excess of large mononuclear cells which for the most part looked misty. However, they were considerably smaller than the large mononuclears present in the blood of Plimmer and Miles. A good many degenerated forms were seen. Most of the cells and nuclei had an even round contour, and vacuolation was present in the majority. The nuclei showed an appearance of basophile granulation and were stained lightly. The protoplasm of the vast majority was hyaline and faintly basophile. Some showed basophile protoplasm with an indefinite appearance of basophile (azur) granulation. A few had faintly acidophile protoplasm. Few cells possessed much protoplasm, the nucleus as a rule making up five-sixths of the cell. Some cells showed reniform nuclei. A few showed signs of proliferation. These mononuclear cells

varied up to four times the size of a red blood corpuscle; the majority were two to two-and-a-half times the size. The polymorphs were small and took the stain badly. There was no poikilocytosis and no nucleated red cells were seen.

Marrow smears. The white cells were practically identical with those in the blood, with the exception that no degenerated forms were noticed. They consisted almost entirely of large mononuclear cells. The residue was made up of a few brightly staining cells about the size of a red blood corpuscle, which resembled lymphocytes. A very few neutrophile myelocytes and cells with reniform nuclei were also seen.

Lymphatic gland. There was practically no distinction between cortex and medulla, while the trabeculae and lymph channels were but feebly represented. The whole gland consisted of masses of lymphocytes with occasional traces of fibrous trabeculae. The whole was surrounded by a condensed connective tissue capsule; between this and the lymphoid tissue an indefinite lymph channel was visible. A few cells resembling type 1 were seen. There were practically no cells of type 2, and the absence of haemorrhages was a marked feature. This was practically a normal gland, for in some lymph glands the fibrous trabeculae are very slightly developed so that the gland seems in section to be an almost uniform mass of lymphoid tissue (see Schafer's *Histology*, p. 172). The gland examined was taken from the axilla and was the largest one present. Unfortunately I was not able to examine other glands to see whether this condition prevailed throughout.

Spleen. The capsule and trabeculae were normal. Some vessels looked degenerated, but no infiltration of their coats was to be seen. The Malpighian bodies were poorly marked, being represented by a few dark lymphocytes round the arteries. However, the organ was densely infiltrated with mononuclear cells. Most of these were from one-and-a-half to two red blood corpuscles in size and differed from lymphocytes in having a lighter nucleus and rather more protoplasm. A good many cells corresponding to type 1 were present—some proliferating. There were not so many red blood corpuscles as usual. Some, but not many, endothelioid cells and a few pulp cells were noticed.

Liver. Far fewer cells in Glisson's capsule than in the other cases. These for the most part resembled large lymphocytes—a few cells corresponding to type 1 were present. Some degenerative change was seen in the vessels. The veins showed some infiltration of their walls, and these had ruptured in places. Only one cell was seen containing two nuclei. The liver substance was much degenerated.

Kidney. A few subcapsular deposits spreading inwards between the tubules. However, these were not well marked. Some vascular degeneration was present. A few hyaline and epithelial casts were seen in the lumen of the tubules, which latter showed marked signs of degeneration in many cases.

Brain. Under the low power dense round masses of mononuclear cells surrounded by a zone of degenerated brain tissue and red blood corpuscles. The average size of these masses was about a quarter of a field. Between them

comparatively normal brain tissue was present. Many cells were comparatively small and had little protoplasm. Some of type 1 were seen, usually with scanty protoplasm. A few cells of type 2 were noticed, also one or two with reniform nuclei. At the periphery the cells were as dense as at the centre in the great majority of cases. In places they were much less dense at the periphery, being mingled with degenerated red blood cells and the debris of nerves. It is to be supposed that capillary degeneration and rupture was followed by small extravasations of blood. In the effused blood the cells had evidently proliferated, displacing the cerebral matter and red blood corpuscles. In some places fresh minute capillary extravasations had occurred at the periphery of the proliferating mass. Probably owing to the cells having little protoplasm the deposits remained markedly localized.

Case IV.

Eva Powell, aged 18 years, single, was admitted to the London Hospital on April 21, 1907. She had had influenza, but no other disease before the present illness. For one month she had been unwell. The illness started with a chill, and the next day spots appeared on the skin. A week later pains started in the ankles, knees, wrists, and fingers, but none of these joints were swelled. A week previous bleeding from the nose commenced.

On admission to the hospital she was very anaemic. The skin was white, and she had red purpuric spots all over the body. She had frequent attacks of epistaxis. The lymph-glands were not enlarged. The tibiae were greatly curved anteriorly, due probably to rickets. The respirations were 26 a minute, and a few scattered rhonchi were heard in the chest, otherwise the lungs were normal. The pulse was rapid, 140 per minute, soft, and of low tension. There was a visible pulsation in the neck. The apex-beat was in the fourth intercostal space, in the mid-clavicular line. The area of cardiac dullness was slightly diminished. A haemic murmur was audible over the base of the heart, otherwise the sounds were normal. There were sordes on the teeth, the breath was foul, but the tongue clean. The spleen was palpable, but the liver was not felt. Neither knee-jerks nor plantar reflexes were obtained, but occasional pseudo ankle clonus was noticed. The urine was amber-coloured, sp. gr. 1,020, and contained no albumin. On April 24 the patient was weaker, and the temperature 102·2°.

Blood count.	Reds	1,500,000
	Whites	570,000
Differential count.	Large mononuclear cells . . .	86 %
	Small do. (resembling lymphocytes) .	13·95 %
	Polymorphs	·05 %

The patient died at 12 midnight from uncontrollable epistaxis, and general asthenia.

Post-mortem. The body weighed 5 st. 7 lb., and was 5 ft. 1 in. in length.

External appearances. The skin was a pale, yellowish-grey, and the lips a very pale blue. On the neck, shoulders, arms, thighs, and legs were scattered discrete red ecchymoses, but there were none on the back. They had a light centre, and varied in size from a pin-point to two pin-heads. The tibiae were sabre-shaped with the sharp convexity pointing forwards, and slightly outwards. The bridge of the nose was well-formed. Some of the molar teeth were carious. There was blood in the nares. The palate was narrow and high. There were palpable glands in the groins and axillae. The breasts were small, but otherwise normal.

Thorax. There were some easily broken down adhesions at left apex, but there was no free fluid. The anterior mediastinum contained a very little fat. The bilobed thymus extended from the cricoid ring on to the left auricle (about 4 in. by $\frac{3}{4}$ in.). The cut surface showed lobulation, and was very pale.

The pericardial sac contained 2 oz. of clear, straw-coloured fluid. The surface was smooth and glistening. The heart weighed 8 oz. The surface was covered with ecchymoses. On the anterior surface, close to the apex, was a white, fibrinous tag. The right heart contained a pale, gelatinous clot. The valves were smooth and translucent with the exception of two small yellow thickenings on the anterior flap of the mitral. There were many small, sub-endocardial haemorrhages. The interior of the right ventricle showed well-marked tabby-cat striation.

The deep cervical glands were up to the size of a cherry-stone; the cut surface was pinkish-grey, and oedematous. The glands of the posterior triangle were up to twice the size of a cherry-stone; the cut surface was fleshy, red, and oedematous.

The bronchial glands were about the size of almonds; the cut surface was flecked with black. Two chalky-white areas were found. The axillary glands were somewhat larger on the right side—up to an almond in size. The cut surface was yellowish-grey, and showed distinct vessels. The glands felt abnormally hard. The tonsils were slightly swollen; the cut surface showed dilated crypts.

The left lung was crepitant throughout. Anteriorly it was a very pale slate colour, but posteriorly it was stained a blood-red. On the surface of both lobes were some raised haemorrhagic areas, nodular to the touch. The cut surface was pale, and showed numerous slightly-raised haemorrhagic and almost airless areas, which corresponded to the nodules on the surface. A clear fluid flowed spontaneously from both lungs. The right lung showed the same changes as the left. The bronchial mucous membrane was very pale.

Abdomen. The spleen weighed 12 oz. It was large, and very flabby. The cut surface was of a uniform brick-red. The trabeculae were visible, but the Malpighian corpuscles were very small and indistinct. The mesenteric glands equalled the size of two peas; the cut surface was yellow and smooth. The mucous membrane of the stomach showed post-mortem digestion at the fundus, and numerous punctiform submucous haemorrhages all over. The gastro-

hepatic glands were very slightly enlarged. The cut surface was a pale grey, and dotted with small haemorrhages. The liver weighed 3 lb. 12 oz. It was flabby, and the cut surface was moist, swollen, and of a pale yellow colour. Glisson's sheaths appeared broad, distinct, and of a bluish-white colour. The liver substance was fairly soft, and friable.

The left kidney was moderately firm to the feel. The capsule was thin, and stripped off readily. The surface was smooth, and of a pinkish-yellow colour. There were numerous slightly-raised haemorrhagic spots. The ratio of the cortex to the medulla was 1 : 2½. The cut surface of the former was of a pale yellow colour with an indistinct vertical pattern; the latter was similar in colour, with indistinct vasa recti. Between the medulla and cortex was an irregular white line projecting above the surface. Small haemorrhagic areas, the size of a pin's head, could be seen in the cortex. The right kidney was somewhat smaller, and in the demarcation zone were discrete, round, raised, white nodules, many with haemorrhagic areas. The lumbar glands were small. Many showed anthracosis. The inguinal glands were the size of haricot beans. The cut surfaces were smooth, and a yellowish-grey colour. There was a small ulcer of the rectum near the anus, with a slough on the surface, which was surrounded by haemorrhage. The bladder was healthy. The uterus and cervix contained a thin red clot. The intestines were a very pale slate colour. The peritoneum was smooth and glistening, and showed a very few minute subserous haemorrhages. The intestines contained a black material. Peyer's patches were very small.

The skull-cap was of moderate thickness. The dura was thickened, oedematous, and showed numerous small haemorrhages both on the outer and inner surfaces. The superior longitudinal sinus contained a gelatinous post-mortem clot. The other sinuses were free from clot. The vessels of the brain were healthy. The brain substance was firm and very pale. The ventricles contained a little free fluid. The cut surface was moist. The pituitary body was rather large.

Bones. The right femur was short and thick. The neck was at right angles to the shaft, which was bent forwards and outwards. The marrow was of a deep red colour throughout, with the exception of one small, gelatinous area near the centre. The sternal marrow was red throughout. The marrow of the ribs and vertebrae was similar.

Microscopical examination.

Blood count. Reds 1,500,000
Whites 570,000

Differential count with $\frac{1}{12}$ obj.

Mononuclears larger than a red blood cell . . .	92·45 %
Small do. (resembling lymphocytes)	6·32 %
Degenerated forms	1·45 %
Polymorphs (normal)	·54 %

The mononuclear cells took the stain fairly well. The vast majority were larger than normal lymphocytes, but none were larger than three-and-a-half, and few larger than two-and-a-half red blood corpuscles. The majority were about one-and-a-half times that size. Many of the large cells seemed to be proliferating. The protoplasm was distinguishable in very few cells. The majority of the nuclei looked granular and finely vacuolated. As a rule, the cells appeared as fairly homogeneous rather dark blue spheres. The large ones were indistinguishable from the small except by their size. As a rule, the nuclei of the larger cells stained more faintly than the smaller, while vacuolation was more marked. One mononuclear was seen containing a few neutrophile granules, and one with doubtful eosinophile granulation. One cell was also seen with a reniform nucleus and hyaline protoplasm. Some poikilocytosis and polychromatophilia was noticed. A few normoblasts were present.

Marrow. In smears of the marrow 95 per cent. of the cells present were of the mononuclear variety. They showed little protoplasm and no granules. They varied from one-and-a-third to twice the size of a normocyte. There were a few dark lymphocytes about the size of a red blood cell. Two polymorphs and one eosinophile leucocyte were seen. Numerous normocytes and normoblasts were present. Sections showed a good many cells conforming to type 1, as a rule with little protoplasm. Some fat cells were also noticed.

Glands. In no gland was there infiltration of the capsule. In the cervical glands there were irregular areas of dark lymphoid tissue, separated by trabeculae and lymph sinuses. Lymphoid tissue was rather scanty in the medulla. Some of the smaller vessels were distended with lymphocytes. No germinal centres were noticed. Some of the trabeculae appeared to be infiltrated. The lymphoid areas contained lymphocytes of normal appearance. There were a few mononuclear eosinophile cells. No definite structure was found in the axillary glands. Lymphocytes were evenly distributed. One mononuclear eosinophile was seen. Many of the small vessels were plugged with fibrin. One inguinal gland was fibriotic, and the lymphoid tissue was much reduced in amount.

The spleen was densely infiltrated with what appeared to be lymphocytes of the normal type—a few were large (type 1). The trabeculae and vessels appeared normal. There were occasional mononuclear eosinophiles, but no typical Malpighian bodies. Many endothelioid and one giant endothelioid cell were noticed. The trabeculae were normal.

The connected tissue of the thymus was oedematous. Many Hassall's corpuscles were seen, some small with a central hyaline plug, others large and apparently cystic. The small ones were composed of epithelial cells, with sausage-shaped nuclei. Sometimes these had fused together. The larger cystic ones were lined by a layer of similar cells. Many cells resembling lymphocytes were seen. The vessels were crowded with similar cells. In the neighbourhood of Hassall's corpuscles were cells with larger, clearer, finely-reticulated nuclei, with a varying amount of pale protoplasm. Occasional small mononuclear eosinophiles were seen.

Lung. The capillaries and venules were crowded with cells resembling lymphocytes. Extravasated blood was seen in many of the bronchioles.

Liver. Glisson's capsule was full of small, mononuclear cells. Some of the small vessels were degenerated, and there was occasional infiltration of the vessel wall. The liver substance was in an advanced stage of cloudy swelling. Many small aggregations of liver cells were surrounded by lymphocytes. There were a few cells corresponding to type 1.

Kidney. A few subcapsular collections of small mononuclear cells. There was a broad, irregular band of infiltration in boundary zone; also round areas in the deeper portions of cortex, between the tubules. These were often linked by connecting strands of cells to the cells in the boundary zone. There were many small haemorrhages, but comparatively few cells corresponding to type 1. The kidney substance showed the usual degenerative changes.

Summary of a few interesting pathological points of similarity and difference in these four cases.

1. All cases showed small multiple haemorrhages in the various organs.

2. In the three cases in which the marrow was examined, it was increased in amount. The colour varied. It was either grey, pink, or red, the depth of colour depending on (*a*) the amount of blood in the marrow capillaries, but chiefly on (*b*) the amount of haemorrhage into the marrow substance. The marrow showed marked alterations in the three cases in which it was examined. In Banks and Powell practically all the white cells were non-granular mononuclear cells larger than a red blood cell. In Plimmer there was a fair proportion of granulated cells, although in most cases the granules were exceedingly minute. In the two cases of chloroma the cells were larger and possessed more protoplasm, both in the blood and in the tissues, and there were indications of the presence of atypical myelocytes in both. Large mononuclear cells with reniform nuclei and a large quantity of hyaline protoplasm opposite the dent in the nucleus, were a feature in both. These cells were extremely rare in Powell, while a few were seen in the blood and marrow of Banks. It is to be noted that somewhat similar cells are described in normal marrow.

3. The spleen and liver were somewhat enlarged in all four cases; also the liver was markedly affected, and this was especially noticeable in Plimmer and Miles. Glisson's capsule was infiltrated and there was also vascular degeneration. Speaking generally, vascular degeneration was more marked in Plimmer and Miles, and many of the small blood-vessels were infiltrated by mononuclear cells in these two cases.

4. The glands were hardly enlarged at all in Banks and Powell; they were definitely enlarged and many were green in Plimmer and Miles. In these two cases the trabeculae and pericapsular fat were infiltrated by mononuclear cells.

5. Endothelioid proliferation as a rule was not marked in the affected tissues. An exception to this statement must be made in the case of Plimmer. Here, endothelial proliferation was very marked in the cervical glands and also in the buccal and pharyngeal lymphoid tissue. This endothelial proliferation was nothing like so well marked in the other glands examined. The mouth was very septic some days before death and the tonsils were ulcerated. Smears from the latter showed countless diplococci though no organisms were noticed in the sections. This multiplication of endothelioid cells was evidently due to the toxins produced by the cocci.

6. The thymus was present in three cases out of four. Its persistence in Powell and especially in Plimmer was noteworthy.

Organisms were carefully looked for in the blood and tissues of all four cases, but none were seen. No culture media were inoculated. The haemoglobin index was not recorded. If the percentage of haemoglobin had been estimated, it would have been quite valueless, as present methods do not record the true index in these cases, the index varying 'pari passu' with the leucocytosis.

Degenerated cells were present in the blood of all four cases. Their numbers varied directly as the temperature:—

Plimmer. On April 26, 1907. Temp. 101·2° both morning and evening.

Total leucocytosis	240,000
Degenerated forms	5%
No. of degenerated forms per c. mm.	12,000

Miles. April 5, 1906. Temp. 101°–105°.

Total leucocytosis	320,000
Degenerated forms	50%
No. of degenerated forms per c. mm.	160,000

Banks.	Temp.	Degen. forms.	Total leucocytosis.	Degen. forms per c. mm.
June 12, 1906.	102·6°–103°	32%	50,000	16,000.
„ 13, „	101 –101·6			
„ 14, „	100 –100·6			
„ 15, „	99·8 – 99·8	13·5%	121,000	16,351.
„ 16, „	99 – 99			
„ 17, „	99 –103			
„ 18, „	102 –104	14·59%	180,000	26,262.

Powell. April 24, 1907. Temp. 97·8°.

Total leucocytosis	570,000
Degenerated forms	1·45%
No. of degenerated forms per c. mm.	3,931.

In another case of acute leukaemia these data were obtained over a period of several weeks, while the daily output of uric acid was also estimated. The number of degenerated cells increased with the temperature, and their number grew less (with one exception) when the temperature fell. The amount of uric acid excreted bore no relation either to the temperature or to the number of degenerated cells present. Probably the rise of temperature (at any rate in part) is due to the absorption of nucleins, albumoses, &c., from the broken-down cells in the blood. This seems to affect the thermogenic apparatus in some way, and is probably similar in origin to aseptic traumatic fever. Perhaps an extended series of observations would show that this relationship is not so constant as it appears to be. However, these data prove that degenerating cells in the blood exercise an important influence over the temperature. Previously, the presence of these degenerated forms has been ascribed to imperfect technique in making the films, but this is obviously a factor of no importance when their number varies so tremendously in different cases. Even if the imperfect technique be granted, one has to admit that some cells are more likely than others to become crushed in making the film. Moreover, many of the degenerating forms react differently to the stain, e. g. with Leishman's stain they are tinted a mauve colour.

It would be interesting to examine leukaemic cells for 'heterotype mitoses'. According to Lövit the undifferentiated marrow cells do not normally divide by mitosis. In these cases cells were seen dividing, apparently by direct division.

The chief omissions in these cases were the following:—

1. Ehrlich's triacid stain, which is the best for neutrophile and eosinophile granules, should have been employed.

2. The marrow was not examined in Miles. However, the blood in these cases seems to be a rough mirror of the cells in the marrow, so that the omission, although serious, was not irremediable.

Before discussing the pathology, the points of similarity and difference between chloroma and acute lymphatic leukaemia will be briefly summarized.

Resemblances between chloroma and acute lymphatic leukaemia.

First of all, the two diseases agree as regards age and sex. In the last 16 cases of acute lymphatic leukaemia at the London Hospital, 11 were males and 5 were females. The average age was 21·5 years. In Dock's first series of 16 cases of chloroma (i. e. cases reported up to 1893), 10 were males and 6 females. The average age was 18·8 years. In his second series of 23 cases (between 1893 and 1904), 19 were males and 4 females. The average age was 15·2 years. In a further series of 8 more recent cases (including the two present ones), 5 were males and 3 females. The average age was 18·8 years. This gives a grand total of 47 cases of chloroma, of which 33 were males and 14 females, while the average age was 17·6 years.

Both diseases usually appear before puberty and become progressively more

rare with advancing age. The symptomatology in both conditions is very similar. The following symptoms and changes occur in both: Weakness, marked anaemia, haemorrhagic tendency, splenic and glandular enlargement (usually slight); also metastases in the liver, kidneys, and less frequently in the lungs. In chloroma, secondary deposits commonly occur in the orbits, temporal regions, and other cranial bones; also in the prevertebral tissue, skin, and other organs where lymphoid tissue does not normally exist. However, non-chloromatous growth sometimes occurs in these situations in association with lymphatic leukaemia.

Histological comparison between chloroma and acute lymphatic leukaemia.

Looking at these diseases from the point of view of morbid histology, there are several differences between the two conditions.

These may be summarized as follows:—

1. In chloroma, infiltration of the walls of the small blood-vessels is more marked.

2. Metastases are more frequent.

3. The eroding power of the cells is greater, for bone and nerves may be infiltrated and destroyed in some cases, while the periglandular connective tissue of lymph nodes is usually infiltrated. These changes are far more limited in acute lymphatic leukaemia.

4. In chloroma the cells are on the whole larger and possess more protoplasm, both in the blood, the marrow, and the tissues.

Bearing these facts in mind it may be stated that increased pathological malignancy may be accounted for by the additional quantity of protoplasm in the morbific cells increasing their amoeboid powers. (Compare brain of Banks with the infiltrations in Plimmer and Miles.) Accordingly it may be stated that in acute lymphatic leukaemia haemorrhages are usually necessary for the production of infiltrations, while in chloroma the cells in many cases seem to make their way through a degenerated vessel wall. In this connexion it must be noted that increased pathological malignancy does not mean a shorter clinical course; this seems to depend largely on the secondary anaemia. The average duration of a case of chloroma is longer than one of acute leukaemia. In most cases of chloroma the primary lesion is more focal. Accordingly anaemia develops more slowly, and the case is clinically less acute.

Seat of primary growth in chloroma and acute lymphatic leukaemia.

Where is the primary growth in chloroma? In Dock's analysis of 23 cases gathered from the literature, some part of the head was affected in all but two. In many of these cases the growth seems to have primarily originated in the cranial bones. In two cases the vertebrae were first affected.

In Dock's case Warthin says: 'On stripping back the prevertebral tissues,

flattened greenish masses, 4–10 mm. thick, were discovered. The marrow spaces of the vertebral bodies were increased in size, while the red marrow was replaced by a greenish pyoid marrow. On cutting into the vertebrae, direct connexion could be seen in many places between the greenish tissue surrounding the vertebral bodies and the greenish marrow of the enlarged spaces. Sections made through the prevertebral green tissue and vetebrae showed that the large masses of cells in the enlarged marrow spaces were, in many cases, directly continuous with the periosteal infiltration by means of relatively large openings in the bone. In some places masses of cells had grown or collected beneath the periosteum, raising it from the bone.' He concludes that in this case the primary growth arose within the marrow spaces, and that it grew directly through the lymphatics and blood-vessels, breaking through the bone and involving secondarily the surrounding tissue.

Hichens thus describes the appearance in his case: 'Growths were present in the dura mater which did not infiltrate the brain, but which pitted and slightly eroded the overlying calvarium.' He also describes subperiosteal nodes in the temporal fossae. He offers no explanation, but it seems obvious after reading Dock's paper that the growth originated in the marrow, eroded the inner table of the skull, subsequently giving rise to deposits in the dura. How else can we explain the brain remaining uninvolved? Similarly, these mononuclear cells made their way through the outer table, giving rise to subperiosteal deposits in the temporal regions.

In Dunlop's case there were green deposits in the temporal fossae, on the dura mater, and in the diploë of the cranial bones. The brain was unaffected, but on stripping the infiltrated dura mater, the parietal bones presented a worm-eaten appearance. In the femur the periosteum was a bright green, while the marrow was like greenish pus.

In Tuerk's case there was a diffuse green infiltration of the vertebrae, ribs, sternum, and the proximal ends of the femora. The upper part of one humerus was of a reddish-grey, while the other long bones showed a fatty marrow.

Trevithick, describing the post-mortem appearances in his case, says: 'The sternum was largely involved, showing green subperiosteal nodes and green cancellous tissue. Many ribs were in a similar condition. There were similar hard nodules between the periosteum and the bone, near the sagittal suture. Also similar tumours between the dura and the skull. In some instances the position of these corresponded with nodules on the external surface, while the intervening bone was stained green.' He does not mention any alteration in the surface of the bone. Apparently in most cases the cells grow through the bone without altering its external appearance; this is not to be wondered at when their minute size and, as a rule, slight eroding powers are taken into consideration. In some cases they seem to escape by the lymphatics.

In Hunt's case there were vertebral, sternal, and temporal growths, all of which were subperiosteal. In a case reported by Pope and Reynolds, the subperiosteal situation of the tumours was also noted.

In one case (Klein and Steinhaus) it is expressly stated that the lymphatic glands were without any pathological changes, the growths affecting the periosteum of the bones of the head and trunk, kidneys, prostate, and marrow of the femur.

The initial growth then does not commence indefinitely in the marrow, but arises in the red marrow. After the first year of age this becomes proportionately less, and by puberty is restricted to the bones of the skull, vertebrae, ribs, sternum, and epiphyses of the long bones. Chloromatous growth has been noted in all these situations. The epiphysis of a long bone has never been proved to be the 'fons et origo mali', but as the cells in the cancellous spaces are apparently similar, there seems to be no reason why an epiphysis should not be primarily affected. The marrow of the long bones seems never to have been systematically examined in the doubtful cases, and as the bone in these situations is much thicker than in the tables of the skull, the condition would be much more likely to pass unrecognized.

Does acute lymphatic leukaemia also originate in the marrow?

It most certainly does. Besides the suggestive evidence brought forward when dealing with the origin of chloroma, there is a considerable mass of further evidence. This may be summarized as follows: 1. The marrow is always affected. In the last 16 cases of acute lymphatic leukaemia admitted to the London Hospital, the marrow was examined in 9. In all cases the marrow was increased in amount, while the colour varied. It was usually grey, sometimes pinkish-grey or red. When a microscopical examination was made, over 90 per cent. of the cells were invariably of the marrow lymphocyte type.

2. On the whole, the cells in the infiltrations closely resembled the cells in the marrow and blood. Cells with uniform nuclei and a fair amount of hyaline non-granular protoplasm opposite the dent in the nucleus were seen in the blood, marrow, and tissues of Plimmer, Miles, and Banks; very few were present in the case of Powell. (Buckmaster describes similar cells in normal bone marrow.)

3. The glands and spleen are seldom much enlarged, and then only in the later stages of the disease. In the aforementioned 16 cases the enlargement, both of glands and spleen, was greatest in the more chronic cases. In the most acute, the enlargement was very slight indeed. In Banks this was so, while in another patient the glands were not enlarged at all.

4. The presence of a rapidly progressive secondary anaemia due to deficient haematopoiesis.

5. The experiments of Flexner, who prepared two cytotoxic sera—lymphotoxin and myelotoxin. On injecting myelotoxin the marrow responded with an increased production of granular leucocytes and myelocytes. On injecting lymphotoxin there was an increase of lymphocytes and non-granular mono-

nuclear cells in the marrow. The lymphoid tissue of the body responded to both sera in the same way, i. e. by an increased production of lymphocytes.

6. Buckmaster inoculated the marrow of a rabbit with small rods of Indian ink thickened with gum. This produced the appearance of quantities of cells loaded with pigment in the circulating blood, followed by an accumulation of these in the spleen, liver, kidneys and lungs ; the spleen, liver and kidneys are nearly always infiltrated in acute lymphatic leukaemia, the lungs sometimes. This evidence applies also to chloroma.

In the face of such evidence it seems impossible to imagine the spleen or lymphatic glands ever being the seat of the primary lesion, either in chloroma or in acute lymphatic leukaemia. There is no evidence, theoretical or otherwise, in favour of the primary lesion being in any other organ than the bone marrow.

Perhaps the thymus deserves a word. In both chloroma and acute lymphatic leukaemia the thymus has been found enlarged at the autopsy, even in middle-aged people. It is usually infiltrated with cells of the marrow lymphocyte type, but it is rare for green nodules to develop in its substance. In chloroma, the sternum has been affected without the thymus being present, and ' per contra ', in both conditions the thymus has been found affected without any infiltrations of the surrounding tissues. As a rule the organ contains many lymphocytes, while Hassall's corpuscles are well marked. Probably, when it remains enlarged, it assists the organism in its endeavours to keep the blood in a normal condition.

The only real objection to the marrow being regarded as the seat of the primary growth is the apparent deficiency of lymphocytes in normal marrow. According to Buckmaster, human marrow always contains lymphocytes, and often a large number in the case of children. Moreover, one case of small-celled chronic lymphatic leukaemia has been described in which the bone marrow alone was involved.

In man the medullary fat probably represents a potential source of lymphocyte formation. The proof of this is, first, that it has been observed that after middle-age an increasing number of lymphatic glands become almost entirely converted into fat, while preserving their shape and blood supply. Under any abnormal stress, such as a bacterial invasion or cancerous infiltration, these organs are again rapidly converted into ordinary lymphatic glands. Secondly, that the thymus, before becoming completely atrophied, passes through a fatty stage.

The frequency with which the bones of the skull are involved in chloroma may be briefly considered here. The primary seat of the disease seems to be confined to the places where red marrow alone is found after puberty. This looks as if myelocytic formation is normally confined to these bones. Probably acute lymphatic leukaemia has a greater tendency to originate in the long bones. However, this is by no means proven, as a complete osseous examination with the view of determining the seat of primary growth seems to have been

seldom or never made. The one thing certain is that in acute lymphatic leukaemia the eroding power of the cells is less, so that the tendency towards the formation of subperiosteal tumours is reduced almost to a minimum, the cells reaching the blood by the normal channels and the tissues through capillary haemorrhages. In those intermediate cases of chloroma which most nearly simulate acute lymphatic leukaemia, a similar process takes place, but the walls of the small blood-vessels are infiltrated to a much greater extent, and usually the tissues also. Possibly the construction and relations of the skull cap are a factor in the early appearance of the growth in this situation. Possibly, too, there is a greater chance of spurious cases of chloroma getting into the literature. Epinephroma (sarcoma of the suprarenal) seems to be a clinical entity only recently recognized. In this condition, secondary deposits in the skull are practically constant. I remember seeing one of these cases in the wards which presented a typical appearance of chloroma, i.e. temporal and orbital deposits with a slaty colour of the skin over them, and nothing to account for the lesions. The blood merely showed the presence of marked secondary anaemia. However, the case was confidently diagnosed as one of 'malnutrition chloroma', due to rickets or congenital syphilis! Only the autopsy revealed the true state of affairs. If for any reason a post-mortem had not been possible, it is easy to imagine this case being published as an abnormal form of chloroma.

Atypical forms of these diseases and of myelogenous leukaemia.

Let us first consider some of the more atypical forms of chloroma and lymphatic leukaemia. Every symptom and sign present in lymphatic leukaemia, even in the atypical forms, may have its counterpart in chloroma, and the converse also holds good. Two cases are described in the literature which showed the typical picture of chloroma, while the green colour was absent in the lesions. One case was described by Birk. The illness began with weakness, headache, intermittent pyrexia, and enlargement of the liver and spleen. The glands then became enlarged and there was pain over the sternum. The blood showed one red to three white corpuscles. The reds were smaller than whites with few exceptions. Bilateral exophthalmos came on suddenly, accompanied by loss of sight, and after the appearance of oedema in the lower extremities the patient died. After death uniform infiltrations were found in various parts of the body; the exophthalmos was due to the presence of lymphomata. None of the lesions were green. The other case was described by Leber in the following words: 'There were large tumours on the eyelids, going back into the orbits and not adherent to its margin. Both eyes were prominent, and there were swellings under the temporal muscles. Finally, the cervical lymphatic glands became enlarged, while the manubrium was somewhat thickened and painful. The patient was anaemic and wasted. White and red cells were present in almost equal numbers in the blood, the majority being

small. All the swellings increased in size, and the spleen and submaxillary glands enlarged shortly before death. The patient died fourteen months after the tumour first appeared in the orbit, and six months after the leukaemia was recognized!' The lymphomatous tissue removed was not green, otherwise the resemblance to chloroma was remarkable. Unfortunately an autopsy was not held. The significance of these cases will be discussed later.

Even the so-called aleukaemic chloroma, in which the aleukaemia has been described as a diagnostic point between the two conditions, has its counterpart in lymphatic leukaemia.

In these conditions unstained films may show nothing abnormal, but in stained films 90 per cent. or more of the white cells present are of the large mononuclear type. In three cases of acute lymphatic leukaemia out of eleven at the London Hospital in which a blood count was made, the highest leucocytosis was under 30,000 per c. mm.

In Wende's case of lymphatic leukaemia a lymphoma in the temporal region was the first abnormality noticed, i.e. the first evidence of disease was the development of a lymphoma in which lymphoid tissue does not normally exist. Small lymphomata appeared in the region of the sternum and a large one in the left breast two-and-a-half months later, but the blood still showed no marked abnormality. Some weeks later the superficial glands showed signs of enlargement. Definite leukaemia was only noticed three weeks before death. The white cells never exceeded 45,000 per c. mm., of which, however, 97 per cent. were lymphocytes, chiefly small. Many more cutaneous lymphomata made their appearance and the patient became more debilitated. The gums and tonsils became greatly swollen and later ulcerated. Enlargement of the spleen was only noticed a few days before death. In the later stages the anaemia was markedly progressive, the red count being only 803,000 per c. mm. just before death. The same count showed only 1,600 white cells per c. mm. Apparently this was due to a streptococcal infection, these organisms being cultivated post mortem from many parts of the body, and during life from the blood. During the last few days of life there was a marked increase in the uric acid excretion. At the autopsy, none of the lesions showed a green colour. Only the marrow of the sternum was examined. This was paler than normal, and contained some lymphoid cells similar to those in the lesions. This remarkable case closely resembles Bramwell's case of chloroma. In this case the white cells never exceeded 13,000 per c. mm., of which however 95 per cent. were of the mononuclear type (nearly all large). The reds never went below 3,600,000 per c. mm.

However, there were marked secondary deposits, the skin being infiltrated with lymphoid nodules all over. Swellings appeared in the temporal regions, and the tonsils and gums became swollen and ulcerated. Glandular enlargement was not marked, although an enlarged angular gland was the first thing noticed. The spleen was never palpable although the splenic dullness became increased.

At the post-mortem the buccal lymphoid tissue, the lymphomata over the

upper part of the body, and some of the glands, were green. Some enlarged glands were white. The cutaneous nodules on the lower limbs were of a slaty grey. Unfortunately the skull could not be examined, and the post-mortem was otherwise deficient. Permission for the autopsy was only obtained with great difficulty. A rib was the only bone examined. It was dark red in colour and microscopically showed some, but not very numerous, lymphoid cells, similar to the cells in the infiltrations.

In these cases the primary lesions were probably focal. In cases where the skin is so markedly affected it seems to act as a receptacle for the proliferating marrow cells, largely replacing the spleen, lymphatic glands, and blood in this capacity.

In the case of chloroma described by Sutherland, the colour was most vivid over the vertebrae and in the substance of the glands. Some of the long bones showed a greenish surface. The cancellous tissue of the vertebrae was red, while the marrow of the long bones examined was a reddish grey. The diploe of the skull was of a greyish green. Apparently the colour varies in the marrow like it does in the metastases. Bramwell also describes a case which he calls acute lymphatic leukaemia with green glands.

The two cases described under the heading of chloroma in this series are also of the intermediate type. The exact seat of the primary growth was not ascertained in either. In Plimmer there was a green cellular infiltration of the buccal and pharyngeal lymphoid tissue; the submaxillary and cervical glands were green, several of the axillary glands had a greenish tinge, while most of the other glands were grey or white. Green post-mortem clot was also found. The marrow of the many bones examined was of a pinkish grey with the exception of the femur. In this bone, the upper part was of a pinkish grey, the centre of the shaft was deep red with greyish nodules, while in the lower half the marrow was yellow with deep red areas.

In Miles, the cervical glands were much enlarged and of a bright pea-green colour. The glands all over the body were green, but the colour was not so marked as in the cervical glands. The other tumours and infiltrations were not green. The marrow was not examined. The cranial diploe was not noticeably affected in either case. Possibly the seat of primary growth was in an epiphysis, the condition becoming speedily generalized in the marrow before the glandular enlargement occurred. Possibly a more thorough examination of the bones would have revealed it.

Such cases are of great interest, for they are connecting links between the two conditions. If no autopsy had been made, or if it had been carelessly performed, the condition might have been attributed simply to lymphatic leukaemia in both instances: possibly such cases are less rare than is generally supposed. The green colour seems to depend on the variety and structure of the cellular elements, for there is no case on record of a small-celled leukaemia with green metastases. This will be gone into more fully later.

Myelogenous leukaemia, and the rare (?) intermediate forms between this

condition and lymphatic leukaemia, must be briefly referred to. In chronic myelogenous leukaemia, the primary lesion is now universally admitted to be in the bone marrow. The cases present different features, and further, the blood picture in the same patient may vary from day to day. The following is a rough summary of the changes in the white cells:—

1. The polymorphs and transitional polymorphs are largely increased.

2. There is an abundance of neutrophile myelocytes of various sizes and with a variable amount of neutrophile granulation. Cornil's myelocyte, which is larger and altogether of a more primitive type than the small myelocyte, is usually common. It hardly ever occurs except in this condition. The chief exception to this statement is the marked secondary anaemia of children (Von Jaksch's anaemia), but children admittedly revert easily to primitive types of blood formation.

3. Eosinophiles and eosinophile myelocytes are very constantly present.

4. The mast cells show an absolute increase, and large mononuclear mast cells are also present (basophile myelocytes). In acute myelogenous leukaemia mast cells are absent, i.e. they have reverted to a primitive type.

5. Lymphocytes occur in varying proportions in different cases. In most cases there is an absolute increase in the number of lymphocytes, which has no uniform relationship to the stage of the disease. Probably this is due to the marrow cells causing an irritative lymphocytic hyperplasia in the germinal centres of Flemming.

6. In this condition many myelocytes are deficient in and may entirely lack granules. In the latter case they are practically indistinguishable from the large mononuclear cells present in chloroma. Moreover, the more acute the case, the more of these cells are there present. According to Ewing, they are myelocytes which have not had time to form granules owing to rapid proliferation. However, this explanation would not cover the facts in chloroma as exemplified by Plimmer and Miles.

Spontaneous changes in leukaemic blood. Cases have been observed in which the disease begins with a considerable number of polymorphs, passes through a stage in which myelocytes exist in high proportions, and ends in fulminant form with many large cells deficient or entirely lacking in neutrophile granules. Cases have been reported in which myelogenous leukaemia has passed into the lymphatic variety. They may be accounted for in a similar way. It is significant to note that no changes from lymphatic to myelogenous leukaemia have been reported.

Acute myelogenous leukaemia is a very rare condition indeed. However, cases have been reported from time to time, chiefly by German observers. It may be very difficult to distinguish from acute lymphatic leukaemia. The spleen and glands are but slightly affected. I have only been able to find one case in the hospital records which even approximated to this condition. The patient had been ill for six months and died five days after admission. He had the usual symptoms and signs of acute lymphatic leukaemia, including

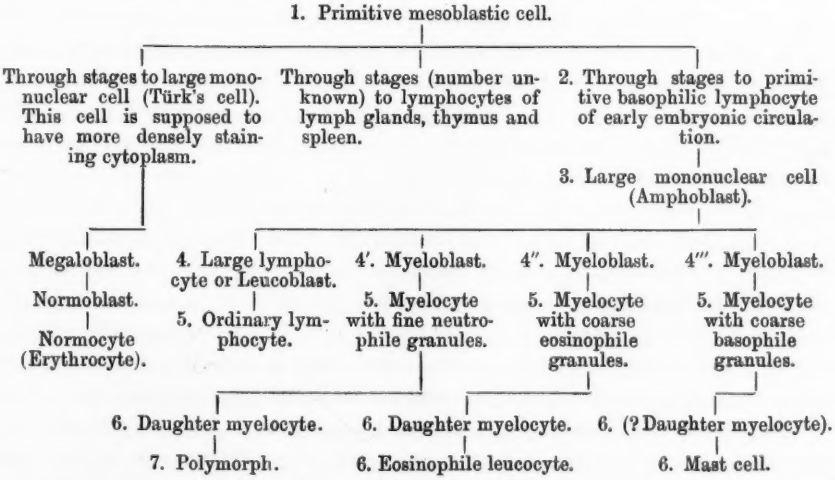
purpura, slight haemoptysis and haematuria. The spleen and liver were just palpable. There was slight glandular enlargement, chiefly affecting the axillary glands. The patient was very anaemic (no blood count was done). A differential white cell count, made the day after admission, showed:—

Large mononuclears	21 %
Lymphocytes	12 %
Myelocytes	52 %
Eosinophiles	10 %
Polymorphs	5 %

Post mortem the liver and cortex of kidneys were studded with small white dots (i. e. leukaemia infiltrations). The spleen weighed 18 oz., the liver 82 oz.

This case was evidently one of those ending in fulminant form. Had the blood been examined again before death a higher percentage of large mononuclear cells would almost certainly have been present. The case may therefore be regarded as one of chronic, ending in acute, myelogenous leukaemia. The proof of the initial chronicity lies in the enlarged spleen. All this clears the ground to some extent for a classification of blood cells with a view to their supposed origin. Some such scheme as the following is a necessary preliminary to the discussion of the cellular morphology of these conditions.

CLASSIFICATION SHOWING THE DEVELOPMENT OF BLOOD CELLS.


1. Primitive mesoblastic cell.
Through stages to large mononuclear cell (Türk's cell). This cell is supposed to have more densely staining cytoplasm.
Through stages (number unknown) to lymphocytes of lymph glands, thymus and spleen.
2. Through stages to primitive basophilic lymphocyte of early embryonic circulation.
3. Large mononuclear cell (Amphoblast).
Megaloblast.
Normoblast.
Normocyte (Erythrocyte).
4. Large lymphocyte or Leucoblast.
5. Ordinary lymphocyte.
4′. Myeloblast.
5. Myelocyte with fine neutrophile granules.
4″. Myeloblast.
5. Myelocyte with coarse eosinophile granules.
4‴. Myeloblast.
5. Myelocyte with coarse basophile granules.
6. Daughter myelocyte.
7. Polymorph.
6. Daughter myelocyte.
6. Eosinophile leucocyte.
6. (? Daughter myelocyte).
6. Mast cell.

Explanation. (*a*) The cells labelled 1, 2, 3, do not occur under normal conditions in the marrow or elsewhere after birth.

(*b*) Cells labelled 4, 4′ &c., seem to occur in scanty numbers in normal bone marrow.

(*c*) In future the cell labelled 4 will be referred to as a leucoblast, the cells labelled 4′, 4″, 4‴, as myeloblasts. These latter, though indistinguishable

from one another microscopically, are evidently specific, at any rate under normal conditions. The leucoblast is best conceived as being a rather large lymphocyte, which is capable of being differentiated morphologically from the myeloblasts and Dürk's cells. The normoblasts, lymphocytes, myelocytes and granular leucocytes are fixed, self-perpetuating types, the myeloblasts and leucoblasts representing potential sources of leucocyte formation.

(*d*) Whether the undifferentiated cell which produces megaloblasts has passed through the same lymphocytic stage or whether it is derived directly from the primitive mesoblastic cell is doubtful. In either case a ready explanation of the anaemia present in acute leukaemia can be given.

(*e*) A few observers have endeavoured to prove that the spleen and lymphatic glands may occasionally produce granular leucocytes. That this occurs would seem to be extremely doubtful and complicates instead of aiding our conception of these diseases.

(*f*) The hyaline cells, which occur in small quantities in normal blood, remain to be considered. The usual view is that they are synonymous with the fixed connective-tissue cells. Probably they may also originate in the lymphatic glands and spleen.

Morphology of the cells present in chloroma and acute lymphatic leukaemia.

Let us first consider the cellular morphology of chloroma. Unfortunately the pathogenic cells in the various organs have seldom been well and thoroughly described, if indeed mentioned at all. However, all observers agree that the mononuclear cells present in the blood are of large size. In the drawings and microphotographs of other cases, apart from the two here described, the size of the cell is a marked feature. It usually seems to be from three to five times the size of a red blood corpuscle and contains rather more protoplasm than the corresponding cells of acute lymphatic leukaemia. This is often more marked in the tissues than in the blood. In both Plimmer and Miles there was reason to suspect that many of these cells were abnormal or degenerate myelocytes. It is also worthy of note that in many cells the neutrophile and eosinophile granules were both few in number and exceedingly small, so that in the majority of cells $\frac{1}{12}$ obj. was necessary to see them at all. A good many cells present showed doubtful neutrophilic granulation and were classed with the undifferentiated mononuclear cells. Let us see how far the literature bears this out.

In Dock's first case large mononuclear cells, similar both as regards size and percentage to the large mononuclears present in Plimmer and Miles, were conspicuous in the blood. In films the protoplasm could not as a rule be distinguished from the nucleus, although no definite granules were made out. The cells were faintly basophile. There were occasional cells with doubtful neutrophilic granulation. The films were stained with methylene-blue and eosin. In hardened sections through the vessels, the cells were seen to contain a good deal of protoplasm. The nuclei were often irregular and sometimes

double. He illustrates the case with very good drawings. Buckmaster describes the blood in a case in which there were only two per cent. of polymorphs. The rest might have been grouped as large lymphocytes,* but by a variety of methods of staining it was possible to identify the majority as myelocytes (i.e. the cells possessed neutrophile or eosinophile granules). He also remarks on the minute size of the granules. Probably many other cases in the literature would have yielded similar results if the time and patience had been forthcoming.

Dunlop. *Differential count.*

Lymphocytes, chiefly large	73 %
Polymorphs	17 %
Myelocytes	5 %
Unclassified and transitional forms resembling myelocytes	5 %

A few days before death a large number of (?) myelocytes appeared in the blood.

Pope and Reynolds. *Differential count.*

Large lymphocytes	19 %
Small lymphocytes	17·5 %
Myelocytes	32 %
Polymorphs	8 %
Mast cells	6·5 %
Eosinophiles	2 %
Unclassified	15 %

The white cells were generally of good shape, with the exception of a few myelocytes which showed irregular or double nuclei and vacuolation of their cytoplasm. In this case Leighton succeeded in demonstrating many cells with both large and small eosinophile granules in hardened sections of the tumours.

Dock's second case of chloroma was very fully worked out. In describing the blood he says: 'The films showed at times many free nuclei up to 18 per 1,000 leucocytes. At other times they were too few to count. These were very small, stained intensely, and showed no protoplasm. The small lymphocytes were unusually typical; however, some showed slight fragmentation of the nucleus (6 %). A small proportion of typical large lymphocytes were present, some of which also showed fragmentation of nucleus (3 %). Marrow lymphocytes, many of which had no visible protoplasm, were present in large numbers (82 %). However, the amount of protoplasm was in some cases comparable to that of the large mononuclears of normal blood. The nuclei stained moderately well with haematoxylin and methylene-blue, faintly with the triacid stain. They looked unevenly blurred in many cases, but in general stained like the nuclei of large lymphocytes. Marked failure to take the stain, and other evidences of degeneration were unusual. The nuclei showed considerable variation in shape. The protoplasm was sometimes ragged at the edges. The protoplasm was blue when treated with Wright's stain. It was sometimes darker than the nucleus, without granulation but with a spongy

appearance. Triacid stained it pale pink or not at all. The distinction from normal large mononuclears was based on—

1. The appearance of the protoplasm.
2. The larger and less district nuclei.

The polymorphs varied much in size, nuclear structure and quantity of protoplasm. There was no marked alteration in the eosinophiles. A few mononuclear eosinophiles were present on two days out of four. Most of them were large, some the size of a red blood corpuscle. The changes in the reds were slight, apart from their scanty number. Warthin examined the tissues in this case. He says: 'The proportion of cells showing distinct protoplasmic body is greater in the infiltrations than in the blood. In the infiltrations a large proportion of cells are granular, the majority containing eosinophile granules in their protoplasm, a small proportion neutrophile, a still smaller proportion distinct basophile. In the majority of fields the eosinophiles are so numerous as to give a red tint to the section. From the numerous transitional forms found everywhere there can be no doubt that the eosinophiles are derived from the large cells of the infiltration. Those eosinophile cells having abundant protoplasm cannot be definitely distinguished from the eosinophile myelocyte. The marrow contains cells of the large lymphocyte type,* the majority showing eosinophile granulation; few red blood cells—few lymphocytes—few polymorphs.'

Klein and Steinhaus state that in their case the majority of cells in the blood were neutrophiles and neutrophile myelocytes. The rest were lymphocytes,* chiefly large (highest count 47 %). The marrow contained non-granular cells and myelocytes, both neutrophile and eosinophile. There were very few cells with polymorphous nuclei. Cells showing eosinophile granulation were present in the tissues. In the other reported cases the blood was either not examined, or described as presenting the characteristics of acute lymphatic leukaemia with a high proportion of large lymphocytes. [When it has not been conclusively proved that these cells are myeloblasts, I prefer to call them large mononuclears rather than lymphocytes, which is a misleading term. In these cases there seems to be little doubt that such cells are true myeloblasts, differing as they do in many ways from normal myelocytes.]

* The demonstration of cells showing eosinophile granulation in the marrow and metastases of several of these cases, coupled with the comparative absence of these cells in the blood, is at first sight a remarkable phenomenon. However, when we consider that the eosinophile is normally a coelomic tissue cell and only occurs in large numbers in the blood in response to a rare but definite chemotactic influence of toxaemic origin (e. g. trichinosis and pemphigus), this absence is explained. On the whole, these cases confirm the view that the vast majority of the cells in chloroma are abnormal forms of myelocytes and myeloblasts. Probably, if smears had been made of the various infiltrations, some granulated cells would have been seen in every case; but it is unreasonable to expect the granules to show up after hardening and staining with

haematoxylin and eosin only. Even under the most favourable conditions (i. e. smears) many of the granules can only be seen with $\frac{1}{12}$ obj. Moreover, it is worth remembering that only in the more recent cases have granules been definitely demonstrated. This is due to improved technique. It is to be noted that granulated cells are extremely hard to demonstrate in the tissues. Smears give the best results. Hardened sections are extremely difficult to treat with blood stains. In the same piece of tissue one observer may demonstrate granules in some of the cells while another observer may fail to do so.

The cells in the affected tissues are of a good size and possess more protoplasm than the cells of acute lymphatic leukaemia. Although not actively amoeboid, they are sufficiently so to enable them to penetrate a degenerated vessel wall. This partly accounts for the greater bulk of the metastases in chloroma, as opposed to acute lymphatic leukaemia. It thus seems likely that the difference between acute myelogenous leukaemia and chloroma is one of degree only. In the former condition the entire marrow is involved at an early date. Accordingly, anaemia is rapidly produced and death takes place before the formation of extensive metastases and green lesions. A typical case of chloroma is much more focal in origin, so that the marrow does not become generally involved before extensive metastases have made their appearance.

The cellular pathology of acute lymphatic leukaemia is a more complex problem still. Granulated cells are rarely found in this disease, and when present, their numbers are very small. When they do exist, marked intestinal lesions are usually present also. Probably the appearance of granulocytes in the blood is due to a toxaemia resulting from secondary infection, the enfeebled marrow responding to the stimulus as best it can. This will also account for the presence of cells with reniform nuclei in the blood of Banks. That the explanation is a reasonable one is shown by the fact that the cells in the infiltrations were smaller than one would have expected from looking at the blood.

In reality it seems probable that the term 'acute lymphatic leukaemia' covers several conditions. In the specimens I have examined, the cells have shown well-marked differences, both in size and appearance, in the various cases. I am inclined to attach considerable importance to the size of the undifferentiated marrow cell in leukaemia conditions. Thus the majority of the cells in chloroma are of large size as compared to the cells present in acute lymphatic leukaemia. This, to my mind, indicates their close relation to myelocytes. In some cases of acute lymphatic leukaemia the predominant cell, though larger than a lymphocyte (i. e. about twice the diameter of a red cell), is comparatively small and has relatively little protoplasm. These cells are probably true leucoblasts. Again, in other cases, the predominant cell is about thrice the diameter of a red cell and has relatively more protoplasm. However, it must always be kept in mind that degenerative processes tend to cause enlargement of the

cell; this is especially noticeable in films and smears. Unless this be remembered, much confusion results, but after making allowances for this, such morphological types certainly occur.

The following varieties of acute lymphatic leukaemia may be hinted at:—

1. A rare condition in which the pathogenic cells are rather small, owing to the predomination of leucoblasts.

2. The more usual larger-celled type, which occurs when the ancestral mother-cell or amphoblast is the origin of the disease. Subacute cases of this type are also occasionally met with. From analogy with other tumours there is no reason why islands of these cells should not remain in the fatty marrow and subsequently undergo malignant metamorphosis.

3. A mixed type, in which myeloblasts, leucoblasts, and amphoblasts occur in varying proportions. Such cases would certainly be difficult or impossible to recognize, but may be presumed to occur from theoretical considerations.

Such a conception of the disease also explains other phenomena. For example, chronic myelogenous leukaemia is much more frequent than chronic lymphatic leukaemia. Accordingly, one would expect the acute myelogenous variety to be at least as common as the acute lymphatic, instead of the converse. But if in reality *true* acute myelogenous and *true* acute lymphatic leukaemia are of approximately equal rarity,—the surplus cases of so-called acute lymphatic being chiefly due to a proliferation of the common mother-cell (amphoblast),—this difficulty largely disappears. Moreover, it must be remembered that acute myelogenous leukaemia may be very difficult to recognize, and if the existence of such a condition be not remembered, the case is likely to be called acute lymphatic or mixed-celled leukaemia. In some cases, moreover, an exact diagnosis cannot be arrived at without an examination of the marrow, and this is not always possible.

Causation of the green colour in chloroma.

The green colour of the lesions in chloroma is a difficult though fascinating problem. In itself it does not constitute a valid objection against chloroma and lymphatic leukaemia being closely allied conditions, as in many cases only a varying proportion of the tumours are green, the remainder being identical in colour with the infiltrations of lymphatic leukaemia. The origin of the colour is, however, a mystery.

Exploded theories are:—

1. That it is due to some pigment allied to bile pigment.

2. That it is due to putrefaction.

Most observers state that the colour fades quickly on exposure to air and light. A few, and among them Warthin, note a temporary increase in the depth of colour. In the case of Miles, the colour quickly disappeared. In the case of Plimmer, the colour remained for several days. The colour fades in preserving solutions, but does not go into solution in the fluids. Huber

ascribed the colour to certain five granules found in the cells, which he thought were allied to if not really a fat. This opinion was shared by Chiari on account of the reaction of the granules seen by him to alcohol, ether and osmic acid. Dock confirms this by finding abundant highly refractive granules in fresh, frozen sections. In sections examined later, when the colour had disappeared, the granules were absent. The reaction to osmic acid, &c., was not stated. Other observers have failed to find these granules. Dunlop, in describing his case, says: 'On the following day all the colour had gone, but on treating the affected organs with reducing agents it partly reappeared, thus indicating the presence of an oxidizable pigment.' Trevithick also found that the colour faded rapidly. He tried reducing agents, but without success. However, hydrogen-peroxide speedily restored the green colour to its original brightness. When removed from the peroxide bath the colour faded, but again returned when treated with the peroxide. A kidney which had been in formalin solution for over two months regained its original green pigmentation in the course of a few minutes. This is remarkable, as hydrogen-peroxide is a powerful reducing agent. Risel found haemosiderin granules, but referred these to the breaking down of red blood corpuscles. He ascribed the green colour to some other substance of haematogenous origin. Reynolds was the only observer who attempted an analysis of the hypothetical pigment. He came to the conclusion that it was of the nature of a fatty acid combined with iron, and that this substance had very strong reducing powers.

It is obvious from the varying nature of the results obtained by different observers that the real cause of the green colour is still shrouded in mystery. In some cases reducing, in other cases oxidizing, substances seem to preponderate in the diseased tissue. Moreover, it seems certain that the green colour is not present from the beginning, and that this colour first appears in the early lesions in the majority of cases. Yet this latter statement does not apply to the secondary involvement of lymphoid tissue in Plimmer and Miles. It therefore seems certain that cellular degeneration plays a part in the formation of the colour. Accordingly, in some cases the age of the growth seems to be responsible, while in others an organic toxaemia facilitates cellular degeneration. On the whole it seems very unlikely that the green colour is derived from ordinary blood pigments. The bright pea-green colour of the chloromatous lesions is much against this view. Although there is a greenish decomposition product of haemoglobin, it is never seen except in cutaneous bruises, and the colour is then somewhat indefinite. It would therefore appear that the atmospheric oxygen is necessary for its production. In cases of acute lymphatic leukaemia a yellowish brown pigment can be demonstrated in varying amounts, especially in the liver. This seldom gives the free iron reaction with potassium-ferrocyanide, but is obviously derived from extravasated blood. In chloroma there usually seems to be more of this pigment. Owing to the longer course of this disease and to its more focal origin, the red blood cells are not so rapidly destroyed and have a longer time in which to multiply and stave

off the threatened anaemia. Accordingly, the sum total of red blood cells destroyed is greater in chloroma, and there is more iron-containing pigment in the tissues in many cases. We have already seen that abnormal myelocytes and myeloblasts are the pathogenic cells in chloroma, and that green lesions never exist in pseudo-leukaemia, lymphosarcoma, and acute lympathic leukaemia, even though there be stomatitis and ulceration of the buccal and pharyngeal lymphoid tissue. Possibly, a degeneration of the granular or pregranular protoplasm of these cells, or an abortive attempt to form granules, is the real source of the colour, aided by the broken-down products of haemoglobin.

The following are the chief data upon which this theory is put forward :—

1. No small, round-celled chloroma has ever been described, though two cases of small-celled leukaemia with temporal deposits, exophthalmos, due to the presence of lymphomata, &c., &c., have been described.

2. In Miller's case lymphomata presenting the characteristics of small, round-celled sarcoma were present in the frontal region and on the dura mater. These tumours were of a reddish yellow. The blood and the other infiltrations consisted of the usual large mononuclear cells. These infiltrations were green, the colour being especially well marked in the kidney.

3. In acute lymphatic leukaemia, necrosis, and ulceration of the buccal and pharyngeal lymphoid tissue is comparatively common, yet no green colour is ever present.

4. The lesions of lymphosarcoma and pseudo-leukaemia are never green.

5. In the case of Plimmer there was marked reaction on the part of the endothelioid cells in the tonsils and cervical lymphatic glands. Moreover, in smears of the tonsil many cocci may be seen. These structures were green. In the other glands examined, the endothelioid reaction was not at all marked, nor were the organs green. The green tissues were also more extensively infiltrated with marrow cells, which possessed more protoplasm and more intercellular substance than in the rest of the lesions. Some of these cells were also connected by protoplasmic processes which were continuous in many cases with the intercellular substance.

6. Dr. Turnbull has seen green marrow in a patient who died of purpura. He thought this was due to some post-mortem change in the medullary fat. However, microscopical examination of the tissue only showed a tremendous hyperplasia of marrow cells, many of which contained neutrophile and eosinophile granules.

Does this peculiar green colour occur in any other tumours?

In Dürk's *Pathology* (1904) it is stated that this pigmentation may be observed in certain sarcomatous tumours, particularly in periosteal sarcoma. I have looked through the last fifty cases of periosteal sarcoma in the hospital records and find no mention of any such pigmentation. Unfortunately, he

describes chloroma as a periosteal sarcoma, which completely stultifies his statement.

Relation of chloroma to chronic lymphatic leukaemia, pseudo-leukaemia, and lymphosarcoma.

To complete the picture, reference to these diseases is necessary. The first question is: Does chronic lymphatic leukaemia also arise in the bone marrow? The verdict must be 'not proven'. Probably it does in the majority of cases. Regarded from a clinical aspect, the more chronic the case the larger the glands and, in most cases, the spleen. The blood shows a marked hyperplasia of lymphocytes, and larger mononuclear cells are also present in most cases. The anaemia is not so marked as in the acute variety, but increases 'pari passu' with the increase of lymphocytes. In a case described by Rosenfeld, the glands and spleen were greatly enlarged, while no post-mortem change was discovered in the marrow examined. Against this, all one can say is that the distribution of the marrow lesions is sometimes irregular, owing to the growth in its early stages being focal rather than diffuse. Ewing quotes a case in which the marrow of the ribs and femur was normal, while the usual mononuclear hyperplasia was present in the bodies of the vertebrae. Moreover, one case of small-celled chronic lymphatic leukaemia has been described in which the bone marrow alone was involved. According to Ewing, the more acute cases show a greater proportion of large mononuclear cells than the more chronic. From theoretical considerations it is what one would expect if the marrow were the seat of the disease. These cells are better formed and show far less degenerative change than the corresponding cells in acute lymphatic leukaemia. There are three cases in the hospital records of apparent chronic lymphatic leukaemia terminating acutely. In two cases haemorrhages only developed two or three days before death; in the other case their occurrence was not mentioned in the history at all, and at the post-mortem there were no haemorrhages or even sub-pericardial petechiae. Unfortunately, in these cases the blood was not thoroughly examined and the mononuclear cells were not differentiated into large and small. All three cases showed marked change in the marrow. When the gland lymphocytes are involved there is nearly always aleukaemia—hence the name pseudo-leukaemia. It is best to restrict Hodgkin's disease to cases in which proliferation of the endothelioid cells of the reticulum and lymph sinuses is the predominating feature. This seems to be of inflammatory origin in the majority of cases, but it may be very hard to distinguish between these cases and endothelioma of lymphatic glands.

Probably chronic lymphatic leukaemia nearly always originates in the marrow. If it were not for Rosenfeld's case, and a case described by Lucke of glandular lymphosarcoma with rupture into a vein and subsequent development of lymphatic leukaemia, one would be tempted to say *always*. However, in the present state of our knowledge, it is impossible to eliminate the glands

and the spleen. Clinically pseudo-leukaemia and lymphosarcoma are often hard to distinguish. The latter appears to be a tumour of somewhat varying malignancy, and there appear to be intermediate forms between the chronic lymphoma and the rapidly-growing infiltrating giant-celled sarcoma. In the majority of cases the glandular swelling remains localized for a considerable time. Gradually other glands are involved, and finally the growth breaks through the capsule and infiltrates surrounding tissues. The metastases frequently partake of the nature of infiltrations. The liver and spleen are not usually involved; in fact, these organs are much more likely to be small, owing to marasmus. The bone marrow is unaffected or, at any rate, not markedly affected. In many cases the reticulum and endothelioid cells are involved, either alone or in addition to the lymphocytes. The presence of leukaemia is a variable factor. When the tumour starts infiltrating surrounding tissues, the lymph paths apparently become blocked, so that there is an absence of leukaemia.

The cases reported by Leber, Wende, and Birk may here be discussed. In Wende's case there were multiple small-celled lymphomata of the skin, while the buccal lymphoid tissue and gums were infiltrated with similar small round cells. The other two cases showed the typical lesions of chloroma, but the diseased tissues were not green and the cells were small.

In these and other cases of small round-celled leukaemia with extensive metastatic deposits which have been described, the primary lesion in the marrow seems to be much more focal. That this is the case is shown by their comparatively long duration, and by the late occurrence of marked anaemia. Whether the focal origin of the disease is sufficient to account for the pathological changes is doubtful. These cases seem to be of lymphosarcomatous nature—at any rate they cannot be distinguished from lymphosarcoma microscopically. Possibly, through some developmental defect, islands of cells corresponding to the primitive basophile lymphocyte remain in the marrow instead of disappearing before birth, and subsequently undergo malignant change. Perhaps in these cases certain marrow cells tend to revert to such a type.

One naturally asks, Why is lymphosarcoma comparatively common in the glands, tonsils, &c., and so rare in the marrow as to be practically non-existent? I attribute this in part to the greater differentiation of the cells formed by the marrow. The leucocytes formed in the glands and other lymphoid tissue have a much shorter genealogical tree than the marrow leucocytes. That this is of importance is proved by the fact that highly-differentiated, mesodermal tissue seldom undergoes sarcomatous change, e.g. muscle. Accordingly, true lymphoid tissue has a better chance of reverting to an embryonic type. Moreover, there is much adventitious and endothelial tissue in lymphoid structures which is capable of undergoing malignant change, so that probably many of the so-called lymphosarcomata have nothing to do with lymphocytes at all.

It has already been mentioned that cells of the myeloblast type alone seem

capable of giving rise to green-coloured lesions. This explains why chloroma never originates in the lymphatic glands, tonsils, or thymus. It is very interesting to note that in Miller's case of chloroma, some of the lesions showed a small round-celled lymphosarcomatosis, and were not green.

Before leaving this part of the subject, a case reported by Osterwald must be mentioned. A patient (aet. 4) showed lesions which had the distribution of chloroma. The marrow of the femur was a greenish brown, the tumours on the dura and in the walls of the transverse and cavernous sinuses were greenish yellow in colour. The other lymphomatous tumours situated on the cranium, ribs, and vertebrae were yellowish or reddish. The growths showed a leukaemic character. Examination of the blood showed three or four red cells to one white (chiefly large). The patient died in less than three months from the commencement.

The following seem to me to be the reasons why the green colour was not more marked in this case:—

1. For chloroma, the case was an acute one. Consequently, there was not time for the green colour properly to develop, nor were organisms present in this case to hasten its development.

2. Possibly the proportion of myeloblasts in the affected tissues was not sufficiently high.

Since it is usual in chloroma for a varying proportion of the lesions to show no green colour, it is theoretically possible to get a fairly acute type of myeloblastic leukaemia, bearing a general resemblance to chloroma, but without green lesions.

Pathogeny of chloroma and leukaemia.

The age incidence in these diseases is of interest and may be briefly considered. We have seen that in chloroma the average age is 17·16 years, in acute lymphatic leukaemia, 21·5 years. Thus the age incidence is roughly the same. Both conditions are more common in childhood, and gradually become rarer with increasing age. In the chronic leukaemias the reverse is the case. In the last 12 cases of chronic lymphatic leukaemia admitted to the London Hospital, the average age was 37·3 years. In 21 cases of chronic myelogenous leukaemia the average age was 37·14 years. In both conditions the disease is uncommon before adult life.

That a difference of nearly 20 years exists in the age incidence between acute and chronic leukaemia is a fact requiring explanation. It will be remembered that in infancy and childhood the marrow is the seat of great activity; but that with advancing age this tissue becomes more and more restricted and quiescent, while the granular cells presumably multiply to a larger and larger extent 'on their own', sufficient being formed under normal conditions for the needs of the organism without the assistance of the myeloblasts, which, like the leucoblasts, eventually assume a resting phase.

Accordingly, the primitive type of cell is, from this point of view, less likely to be affected the older the organism gets.

What is the position of acute leukaemia and chloroma from a neoplastic standpoint?

In the four cases previously described, organisms were not looked for during life; but in the majority of cases in the literature, culture media were inoculated from the blood during life and from the various organs after death. Organisms were hardly ever found, and when present they were nearly always of the septic variety. Löwit claims to have demonstrated protozoa in leukaemic blood and tissues, but his observations have not been confirmed by other observers. Several observers claim to have discovered various 'specific' organisms in acute lymphatic leukaemia, as in neoplasms generally. The investigations of Reynolds are the most interesting. In a case of chloroma he describes a bacillus bearing a marked resemblance to the bacillus mallei, both morphologically and in staining affinities. The distribution of this bacillus corresponded to the distribution of an iron-containing pigment in the affected cells. Endothelioid cells were present in large numbers and were actively phagocytic to this bacillus and to the marrow cells present in the infiltrations. Cultures were unsuccessful, both from the blood taken during life, and from the blood and organs post mortem. Inoculation with blood taken during life was also unsuccessful. He also describes some minute evidences of pigmentation associated with the presence of the same organism, in cases of acute lymphatic leukaemia.

The evidence for and against these diseases being due to an infection may be summarized as follows:—

In favour of infection:

1. The stomatitis, subsequent to swelling of the gums and hyperplasia of the buccal and pharyngeal lymphoid tissue which frequently occurs in acute lymphatic leukaemia. This also occurs in chloroma, but is less constant.

2. The association of a bacillus with the affected cells, and also with an iron-containing pigment in one case of chloroma.

3. The discovery of the same organism in cases of acute lymphatic leukaemia.

4. The very common occurrence of pyrexia.

5. In one solitary instance, leukaemia is reported to have developed in a hospital attendant after nursing a leukaemic patient.

Against infection:

1. Any changes in the mouth and pharynx are always secondary and are not present at the commencement of the disease.

2. As previously stated, the primary lesion always falls on the marrow, both in chloroma and in acute lymphatic leukaemia, but the resulting pathological changes differ entirely from those produced by any known organism. Moreover, a hypothetical chemotactic influence can scarcely be invoked to

explain the appearance of vast numbers of functionless but well-formed cells in the metastases.

3. The absence of inflammatory reaction in the marrow and tissues of these cases is strongly against any organism present being anything but an accidental saprophyte, its powers of growth being increased by the morbid change and loss of function in the affected marrow cells.

In Plimmer, there was certainly a localized endothelial proliferation, but this was explained by the presence of cocci. There is also experimental evidence that these cells do not take part in ordinary inflammatory processes. Neumann induced suppuration in a case of lymphatic leukaemia, and in the pus found exclusively polymorphonuclear cells. The phagocytic action of the endothelioid cells of the lymph spaces towards the cells forming the infiltrations, described by Reynolds, proves nothing either way. One instance of this was noticed in Plimmer, i.e. a giant endothelioid cell, containing a normoblast, some pigment and two mononuclear cells, was seen.

4. The discovery of the same organism in acute lymphatic leukaemia and chloroma is also against it being anything but a saprophyte. As previously pointed out, the two conditions are essentially different.

5. The occurrence of pyrexia, as previously explained, appears to be chiefly due to the products of degenerated marrow cells in the circulation affecting the thermogenic apparatus.

6. The occurrence in the literature of one isolated instance of leukaemia developing in a hospital attendant after nursing a leukaemic patient is, of course, quite valueless. Dozens of cases of 'new growth' occurring under similar circumstances could be collected, such cases being in all probability mere coincidences.

7. The fact that many leukaemic women have given birth to healthy children, is much against the disease being due to an infection. Sanger observed a leukaemic infant, born of a mother who was healthy and remained so. The influence of direct heredity is rare. Casati cites the case of a girl aged 10, whose father and grandmother were leukaemic, while Cameron observed a case in a woman whose grandmother, mother, brother, and two children were leukaemic.

8. The presence of connecting links between leukaemia, pseudo-leukaemia, and lymphosarcoma, e. g. Miller's case in which two of the metastases are described as small round-celled sarcomata, showing irregular blood channels, lined by flattened cells which had evidently replaced the normal capillaries. Several observers have described the metastases as round-celled sarcomata. Also the other abnormal cases of leukaemia and lymphosarcoma which have been previously referred to.

Before any organism can be regarded as pathognomonic, it must conform, at any rate partially, to Koch's postulates. The organism described by Reynolds could not even be cultivated. It seems far more likely that any organisms present are merely accidental parasites, their presence being due to increased

vulnerability of the affected tissues. It may be stated in conclusion that there is no more evidence in favour of the leukaemias being infective in origin, than there is in the case of neoplasms in general.

Acute lymphatic leukaemia has been likened to a fluid sarcoma. In this connexion there is an interesting though poorly investigated case in the hospital records. A girl, aet. 20, was admitted on the surgical side for sarcoma of both breasts (small round-celled). The spleen, together with some lymphatic glands, were enlarged. The tumours recurred, and the patient was admitted about three months later on the medical side. A blood count showed 4,630,000 reds, 120,000 whites. Nearly a month later she developed purpura and quickly died. At the autopsy, the spleen and lymphatic glands were found to be enlarged, and there was a so-called fibrous induration of the pericardium, both pleura, both sides of the diaphragm, and the whole of the mediastinal tissues. The glands throughout the whole body were enlarged, but there was no infiltration of lymphatic tissue in the body besides this. The marrow was not examined. This might have been either a case of lymphatic leukaemia reverting to lympho-sarcoma of bone, or a case of lymphatic leukaemia with independent sarcoma of breast. In either case this patient seemed to have been the subject of a sarcomatous diathesis, and the likelihood of the two diseases being closely allied is well illustrated.

Chloroma, acute lymphatic leukaemia, and that very rare condition—acute myelogenous leukaemia, all seem to be closely allied to the sarcomata. The following objections to the tumours being considered sarcomata, raised by Grünbel, can at any rate be easily refuted. He objected on the following grounds:—

1. The irregular disposition of the invading cells.
2. The poor vascularization of the neoplasms.
3. The impossibility of finding the primary growth.

Let us see if these objections are warranted by facts.

1. With regard to the irregular disposition of the invading cells, it must be remembered that the blood-forming cells of the marrow normally exist in a semi-solid medium, as opposed to the solid and in many cases dense structures in which ordinary sarcomata make their appearance. It would therefore be abnormal and contrary to experience if the metastases showed the solid tumours and dense masses of cells which occur in an ordinary sarcoma. One would expect the cells to be disposed more loosely. Glandular lymphosarcoma, as one might expect, holds an intermediate position with regard to this point. It has previously been pointed out that in primary sarcoma of lymphoid tissue, the secondary deposits often partake of the nature of infiltrations.

2. The poor vascularization of the neoplasms is a small and somewhat feeble objection. In Miles, the metastatic tumours were extremely vascular and contained many capillaries, some of which must have been of new formation.

3. The third objection, as to the impossibility of finding the primary growth, has already been discussed and need not be gone into again.

Real objections to calling these tumours sarcomata do however exist. For instance, one never sees blood channels lined by sarcomatous cells in true leukaemic and chloromatous growths. This, however, is by no means a constant change in sarcomata, and is comparatively rare in lymphosarcoma. Miller describes such a condition in his case of chloroma, both in the growth on the dura and in the deposit over the frontal bone. But I have chosen to regard such tumours as being analogous to glandular lymphosarcoma. There is also another objection, in that cells more or less similar to those occurring in chloroma and acute leukaemia occur in healthy marrow. True they form a minute proportion of the marrow leucocytes, but still they are present. Perhaps, taking all things into consideration, malignant adenoma is the best term to use when arranging the leukaemias with the other new growths.

With regard to the true sarcomata of bone there need be no confusion. They nearly all arise from structures connected with the formation of bone, and attempts at atypical bone formation can usually be demonstrated in the tumours. The exceptions are the endotheliomata, which need no further mention, and the osteitis deformans of Paget and Von Recklinghausen's disease. As regards the two latter, such cases occur in old persons, and the pathological basis of the diseases seems to consist in a reversion of the marrow connective tissue to an embryonic type. Sarcomatous metamorphosis commonly occurs later.

To sum up, acute lymphatic leukaemia is a tumour of malignant nature, arising in the marrow of bones. The growth usually consists of amphoblasts, but leucoblastic and mixed types may occur.

Chloroma is chiefly a tumour of myeoblasts, and arises in the red marrow of bone. Perhaps in some cases all the undifferentiated marrow cells are affected, yet myeloblasts always form the majority. The condition lasts longer than acute leukaemia, owing to the marrow lesion remaining focal for a longer time, thus allowing these cells to form metastases before the marrow is generally affected.

That rare condition, acute myelogenous leukaemia, is of a similar nature. If the disease were more focal in origin and therefore clinically less acute, we should get chloroma. We thus have the apparent paradox of a tumour which is pathologically less malignant, but clinically more malignant.

Chronic myelogenous leukaemia is a tumour affecting myelocytes and to a far less extent the undifferentiated marrow cells which produce them.

Chronic lymphatic leukaemia also originates in the marrow. However, the glands and spleen cannot be positively excluded in every case. It is chiefly a disease of lymphocytes, but amphoblasts sometimes predominate in the sub-acute cases.

Pseudo-leukaemia is a disease affecting the lymphocytes of lymphatic glands.

Myelogenous lymphosarcoma occurs sometimes and is analogous to the cases described by Birk, Leber, Wende and Miller. Possibly it occurs sometimes without co-existing leukaemia, the modes of egress becoming blocked, as is the case in glandular lymphosarcoma.

The present nomenclature of these diseases is confusing and does not indicate the true origin of the affected cells. Yet it is hard to suggest an undoubted improvement. Perhaps the following scheme will make the interrelationships of these diseases clearer.

Lymphosarcoma—glandular, tonsillar, thymic, and myelogenous.

Leucoblastoma, amphoblastoma, mixed. (These correspond to acute lymphatic leukaemia.)

Lymphocytoma—myelogenous and glandular. (These correspond to chronic lymphatic leukaemia and pseudo-leukaemia respectively.)

Myeloblastoma. (This condition includes acute myelogenous leukaemia and chloroma.)

Myelocytoma (chronic myelogenous leukaemia).

In conclusion I wish to thank Drs. Hutchison, Hadley, and F. J. Smith for permission to publish the clinical histories. I am also much indebted to Dr. Turnbull for the autopsy notes and for the loan of sections. I am especially indebted to Mr. Lee for the loan of sections and other valuable assistance.

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DESCRIPTION OF FIGURES.

FIG. 1. From Case I, showing chiefly large mononuclear cells and occasional ghost cells. (Objective $\frac{1}{6}$, Eye-piece No. 5.)

FIG. 2. From Case II, chiefly large mononuclear and degenerate cells. (Objective $\frac{1}{6}$, Eye-piece No. 5.)

FIG. 3. From Case III. The cells are smaller than those from the preceding case. Fewer cells with protoplasm are shown than was actually present. The large cell is a myelocyte, the only one noticed in the film. (Objective $\frac{1}{6}$, Eye-piece No. 5.)

FIG. 4. From Case IV; on the whole there is an undue proportion of cells the size of a red blood corpuscle or smaller. Few of the larger cells are shown. (Objective $\frac{1}{6}$, Eye-piece No. 5.)

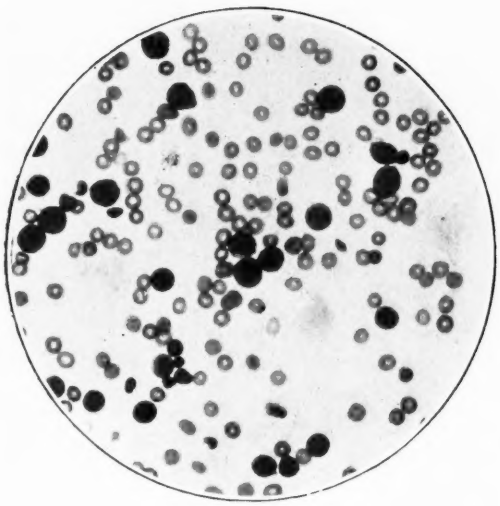

FIG. 1

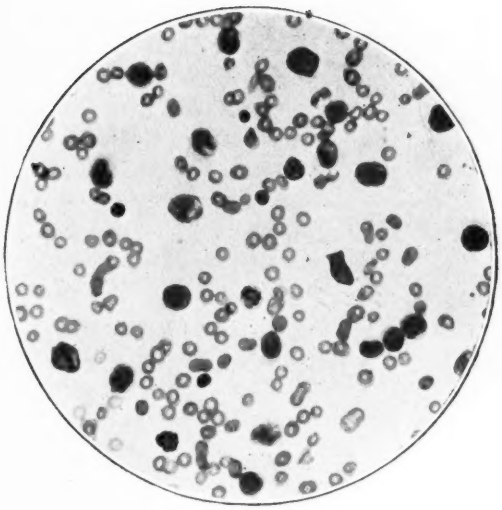

FIG. 2

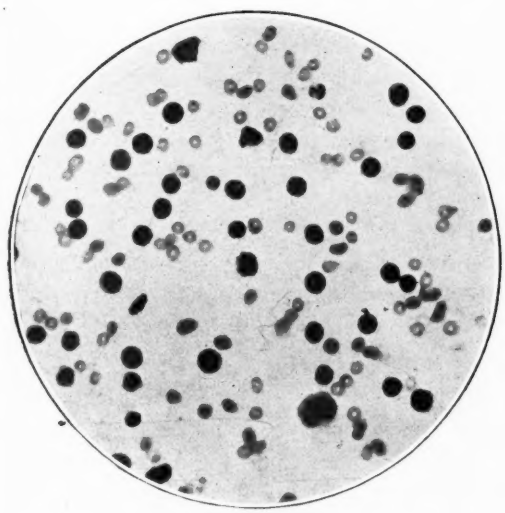

FIG. 3

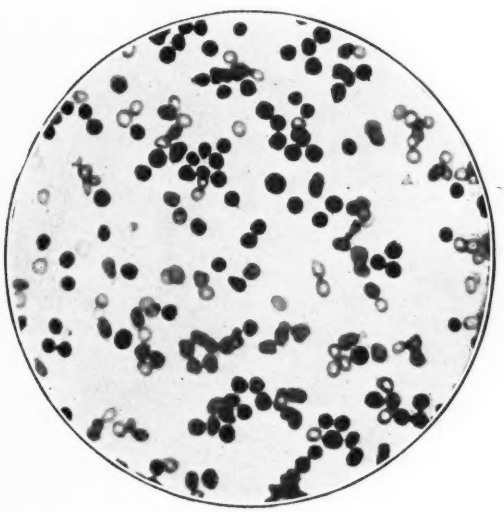

FIG. 4

THE PARATHYROID GLANDS

Part II

THEIR PATHOLOGY IN MAN

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(From the Pathological Laboratory, Charing Cross Hospital.)

PAGE

I. Pathological Changes in the Glands 288

II. The Condition of the Glands in Certain Diseases 295

III. The Rôle of the Parathyroids in Disease 307

The primary object of the investigations described in the last number of this *Journal* was the estimation of the importance of the parathyroid glands in the production of disease, and the following pages will be devoted to the more direct evidence which is furnished by observations on their pathology. This aspect of the question has received but little attention, and among a copious literature on the physiology of the glands definite pathological facts are rare. The results attributed to experimental removal of the parathyroids from animals have been freely applied to clinical conditions, but with few exceptions the essential connecting link, namely a post-mortem or other pathological examination, has not been supplied. The method of argument has been to seek in man some symptom or collection of symptoms comparable to those ascribed to parathyroid ablation and with no further proof to presume that the former depends on parathyroid disease. Thus eclampsia, epilepsy, tetany, paralysis agitans, infantile convulsions, myxoedema with convulsions, exophthalmic goitre, &c. have all been claimed as dependent on parathyroid deficiency, and their treatment by the glandular extract advocated. Whether relief follows or does not follow this administration is of but little importance compared with the results of examining the parathyroids in one single example of each of these diseases.

I therefore propose to exclude from this paper those contributions—interesting and suggestive though many of them are—which omit to support their contentions by evidence obtained directly from the dead-house or operating

[Q. J. M., April, 1908.]

theatre. Those readers who wish to study the more purely clinical aspects of parathyroid insufficiency may be referred to the publications of Alquier, Fruhinsholz and Jeandelize, Gley, Jeandelize, Luzzato, MacCallum, Moussu, &c.

The scope of the paper having been thus restricted, difficulty presented itself in collecting past observations. No paper on the pathology of the glands seems to have been written and therefore references to the subject have not been brought together. It is probable that these are limited in number, and a recent writer found but two papers bearing on the pathological anatomy of the parathyroid glands in man. This number has been increased in the present paper to nearly forty,[1] but some of them have been encountered almost by accident and it is possible that others have escaped notice. I therefore realize that my bibliography may be incomplete though I hope that it will show no serious omissions.

The subject will be treated under three heads: (I) the general pathology of the glands, (II) the condition of the glands in certain diseases, (III) in conclusion, the part played by the parathyroids in disease will be briefly discussed on the foundation laid in the earlier portions of the paper. For convenience of reference, my own observations on each point will be appended to those quoted from previous investigators, and will be distinguished as belonging to 'the present series'.

I. The General Pathology of the Parathyroid Glands.

Congenital absence. Accessory and aberrant glands. The glands are most frequently present to the number of four and the possibility of their complete absence in healthy subjects has obviously an important bearing on their function. Unfortunately, the difficulty of finding all the parathyroid tissue in the neck is so great that its absence can rarely be asserted. On the other hand, many observers who have attempted to find the glands have failed in some instances to discover more than three, two, or one, even after the most careful search, while Rogers and Ferguson record cases in which none could be found. Pepere and Zanfrognini speak of the congenital absence of glands when only two or three were found. Glands in excess of four are sometimes referred to as accessory, but here again the frequent variability of the parathyroids and the fact that the accessory glands are often of the same or even greater size than the remainder, makes the term 'accessory' less applicable than in the case of other organs. According to Rogers and Ferguson a greater or less amount of parathyroid tissue exists as accessory glands in nearly every individual, and aberrant parathyroid tissue is of not infrequent occurrence. The direction in which it may be sought is rarely towards the head—it appears

[1] In addition to these I have found references to four publications to which I have not been able to obtain access. They are (1) Traina, *Boll. d. Soc. Med.-Chir. d. Pavia*, 1905, p. 197, 'Contributo all' anatomia pathologica della tiroide e delle paratiroidi.' (2) Garnier, *Province Méd.*, 1900, Aug. 9, no. 66. (3) *Jour. de Chir. et Ann. Soc. Belge de Chir.*, 1905, vol. v, p. 394. (4) *Ann. de l'Inst. Chir. de Brux.*, 1906, vol. xiii, p. 64.

not to have been encountered at any great distance superior to the oral pole of the thyroid gland—but it has been found as far down as the interior of the thorax. The restriction of parathyroid glands to one special compartment of the deep cervical fascia was noted in Part I of this paper, and as the compartment extends down to the pericardium it is probable that the level of the base of the heart represents the lowest possible limit of aberrant parathyroids.

Haemorrhages. Petersen states that strictly localized haemorrhages can often be recognized, and he attributes their occurrence to the absence of elastic tissue from the small blood-vessels, the walls of which are therefore easily ruptured. Harnett has described in an infant of nine months with whooping-cough and broncho-pneumonia, haemorrhages resulting from rupture of the capillaries during the paroxysms of coughing. In a case of sepsis following rupture of a meningo-myelocele in a new-born child he found haemorrhages scattered through the gland. In the present series this condition was met with in a girl of eight who died with rheumatic endocarditis and pericarditis.

Acute inflammation. No example of this condition appears to have been recorded.

Congestion has been observed (Harnett) in cases of exophthalmic goitre, broncho-pneumonia, diabetes (three cases), convulsions after food poisoning, general peritonitis, septicaemia. In the last instance and in two of the cases of diabetes the congestion was very marked. Hyperaemia and anaemia are regarded by Berkeley as two of the commonest changes in the parathyroids.

In the present series congestion was noted in four cases, namely, chorea of pregnancy, infantile convulsions, phthisis, and typhoid. It should be added that in the case of chorea the congestion was intense and that many lymphatic glands contained large haemorrhages.

Degeneration. The recorded examples of degeneration can be grouped under five heads—amyloid, simple atrophy, fibrous, colloid, and hyaline.

1. Amyloid degeneration of the small blood-vessels was found (Harnett) in a case of old tuberculous hip-disease in which advanced lardaceous change was present in other viscera.

2. An atrophied condition of the parathyroid cells has been recorded by Garnier in some but not in all cases of infectious disease in which he examined the glands. The condition, as Garnier admits, suggests an exhausted state of the cells following over-abundant secretion, in which case 'atrophied' is perhaps hardly the right term to apply. In a case of myxoedema I found two small fibrous bodies near the thyroid gland and these showed slight remains of glandular tissue in so advanced a stage of atrophy that it was not possible to assert whether they represented the remains of accessory thyroids or parathyroid glands.

3. Fibrous degeneration. Berkeley observed a moderate grade of fibrosis in certain of his parathyroids but this condition was never sufficiently marked to lead to destructive changes in the gland tissue except in one case, namely, of paralysis agitans (q.v.). In a patient with phthisis and tuberculous peritonitis

(Harnett), the parathyroids were slightly fibrosed, while in a man of 57, who died from fracture of the spine and presented no marked arterio-sclerosis but definite fibrosis of the thyroid gland, the parathyroids presented a fair amount of interstitial fibrosis. Carnot and Delion observed in a case of phthisis that the internal parathyroids (together with the thyroid) were sclerosed. In the case of myxoedema quoted above the parathyroids showed fibrosis. The present series showed three examples of fibrosis, two being cases of chronic interstitial nephritis and one a case of phthisis.

4. Colloid degeneration. This will be discussed under the heading of cyst-formation.

5. Hyaline degeneration. This change has not hitherto been noted, but was observed in the present series in a case of typhoid fever, and in a child who died from sloughing of the penis after paraphymosis.

Pigmentation. Benjamins observed pigmentary degeneration in the epithelial cells, and Petersen comments on the occasional presence of pigment. He associates its formation with antecedent haemorrhages, and has observed pigment lying actually within the cells, but only when they were in close contact with blood-vessels.

Glycogen formation. The parathyroid glands must be included among the many structures that are known to contain glycogen. It can be demonstrated, according to Petersen, in most freshly teased preparations that have been treated for some hours with a solution of iodine in potassium iodide, and is found often to considerable amount as granules both in the cells and intercellular spaces. It is present at all ages. The explanation of its import and its relation to disease has yet to be settled, but Petersen regarded it as a physiological product though he did not ascertain its condition in pathological states.

Tuberculosis. Benjamins mentions miliary tuberculosis of the parathyroid in a man who died of general tuberculosis. There is one example of a parathyroid gland in a state of tuberculous caseation. It was found by Carnot and Delion in a woman of 24, who died with advanced pulmonary phthisis with multiple cavitation, pneumothorax, fatty degeneration of the liver, &c. Three parathyroids were found, two of which were normal to inspection but sclerosed on microscopical section, though their cells were still healthy in appearance. The third gland, whitish in colour, and the size of a grain of wheat, was adherent to the trachea. Microscopically, almost the entire organ consisted of a caseous mass surrounded by a zone of sclerosis and many giant cells. Carnot and Delion relied for their recognition of the parathyroid nature of the mass on glandular areas at each of its extremities which could be identified as parathyroid tissue in spite of sclerosis and leucocytic infiltration of the epithelium.

New growths and hypertrophy. These are rare. Jeandelize found records of one only. MacCallum described a second and refers to another in addition to that referred to by Jeandelize. The condition is an important one and details of five cases will be given.

1. de Santi, 1900. The first example appears to be that recorded by de

Santi, in which the parathyroid tumour caused symptoms of malignant disease of the larynx. The patient, a man of 58, had vocal laryngeal symptoms and presented a small tumour deeply situated on the right side of the neck at the level of the second and third tracheal rings. The swelling increased to the size of a tangerine orange and was removed by operation. It lay in the inferior carotid triangle and extended beneath the sternum. It was very vascular and enclosed by a capsule to which were adherent the right recurrent nerve and the right inferior thyroid artery. The oesophagus was compressed. The tumour had no connexion with the thyroid gland. Microscopically, there was no sign of malignancy, the structure being that of a normal parathyroid gland but the centre of the growth was occupied by a large cyst.

2. Benjamins, 1902. A solid tumour, almost the size of a child's head and globular in shape, developed in the course of three years in the right thyroid region of a man of 57. It occasioned only local symptoms by pushing the larynx to the left and there was no wasting. On radical removal it was found to be encapsuled and made up of an epithelial mass through which ran a rich connective tissue network. The cells resembled those of a parathyroid but were on the whole larger, their nuclei and protoplasm staining moderately with haematoxylin. Taller cells with more deeply staining nuclei were arranged in pallisade fashion against the connective tissue. Here and there between the cells were small drops of colloid. In the septa ran blood and lymphatic vessels, the latter sometimes containing a colloid substance. In the capsule of the tumour was a normal parathyroid which, however, had no connexion with the growth beneath.

3. Erdheim, 1903. The tumour was found post mortem in a subject (sex not stated) of eighteen years, lying below the lower pole of the right thyroid lobe but not directly connected with the gland. It measured $2\frac{1}{2}$ cm. by $1\frac{1}{2}$ cm., was soft in consistence and its cut surface was reddish-grey. No other parathyroid gland was found. Histologically, the tumour was enveloped in a capsule, and was permeated by a fine connective tissue network bearing blood-vessels and breaking up the parenchyma into strands. The cells, tall or spindle-shaped, lay with their long axes perpendicular to the axes of the strands and, near the surface of the gland, were arranged in palisade fashion. Their protoplasm was fairly plentiful but structureless, the nuclei oval and the cell-walls distinct. Groups of characteristic oxyphile cells and small drops of colloid were observed, while in one place a large cyst, lined by a single layer of epithelium and containing cells in a condition of fatty degeneration, was found. Osmic acid disclosed fat in most of the tumour cells, while near the capsule were follicles enclosing blood and lined by cells containing brownish-red pigment, the product of haemorrhage.

4. MacCallum, 1905. The tumour was found in a man of 26, who died of chronic nephritis. On the right side just below the inferior pole of the thyroid gland, and quite separate from it, was a smooth, round mass enclosed in a delicate capsule and lying in the loose connective tissue. It was

almost spherical in shape and measured 2 cm. in diameter. Externally, and on section, it presented a uniform, opaque, whitish-yellow colour, and was rather soft in consistence. There was a small central cavity, smooth-walled and containing clear fluid. Histologically, oxyphile cells and cells with clear protoplasm were present and in certain parts showed an arrangement in palisade fashion. Mitotic figures were seen. There was no fat and practically no trace of colloid. Except in its bulk the mass differed in no way from a normal parathyroid gland. Its central cavity was lined by flattened epithelial cells and contained 'almost colloid' material. The blood supply of the tumour as compared with that of a parathyroid was extremely meagre. Two normal parathyroids were found, and the thyroid itself was normal.

5. Hulst, 1905. In a very old woman, on the median surface of the right lobe of the thyroid gland close above the isthmus was an oval tumour, 2·5 × 2·5 × 2·0 cm. It was hard, with a dense, whitish, connective-tissue capsule. On section the mass was brownish-yellow like a suprarenal gland and the cut surface was firm, homogeneous and fairly dry. The thyroid gland itself showed senile atrophy. Microscopically, the appearances were uniform throughout. Delicate connective-tissue septa, bearing a rich supply of blood-vessels, divided the polyhedral cells of the tumour into clumps. Some of the cells possessed granular protoplasm staining moderately with eosin, but in others the dark red staining indicated a colloid transformation. The arrangement of the cells was irregular, though often they were grouped in a tubular form, and the lumina contained colloid. Other cells scattered among the foregoing had dark protoplasm and excentrically placed nuclei. Mitotic figures were absent. Small collections of colloid material lay among the cells. There were clusters of lymphocytes and plasma cells on the surface of the tumour. The thyroid gland showed increased connective tissue and its vesicles were for the most part large, some containing colloid but others empty. On the surface of the gland lay a small cluster of cells similar to those in the tumour and probably representing an isolated parathyroid.

Cyst formation. The presence of a colloid material is of frequent occurrence, and has been described by many, from Sandström onwards. As a rule it is seen in minute drops, lying either scattered among the cells or in a central space round which the cells are grouped in a more or less regular formation. Occasionally the drops reach larger proportions and form cystic collections either in the interior of the gland or on its surface. These collections may be large enough to be readily discerned in a stained section by the naked eye.

The derivation and nature of this colloid has received but little attention. Clearly the first question to settle is whether it represents a physiological condition of the glands or a pathological change. In an earlier paper I have given reasons for regarding the former as the correct interpretation and for looking on the colloid as the natural secretion of the parathyroid cells, which, having become swollen with oxyphile granules, extrude this substance into

the intercellular spaces. Here it may aggregate into drops and finally gains the lymphatic vessels in the connective-tissue trabeculae and drains away from the gland. The contrary view—that the colloid is essentially pathological in nature—has been maintained by Welsh, who, however, did not associate the colloid with the protoplasmic granules of the cells. He speaks of 'colloid degeneration' of the parathyroid epithelium, and attributes the colloid that occurs in the centre of an acinus to degenerative changes taking place in the central cells. 'Occasionally,' he continues, 'large cystic spaces filled with colloid are found, . . . but so far from representing a higher stage of the glandular development, they must be regarded as essentially retrograde and degenerative in their character.' This view, however, is not tenable in face of the fact that the whole series of changes in course of secretion have been traced as mentioned above and have been confirmed by Harnett. Further, the conclusion necessarily leads to the assumption that a large proportion of parathyroid glands, both from presumably healthy individuals and from patients suffering from widely separated diseases are in a condition of pathological degeneration. Among 100 cases examined by Petersen, colloid was noted in 25, while of 40 cases of Harnett's it was present in 15 (i.e. 40 %). These figures are the result of examining only a few sections of each gland and would certainly have been larger had serial sections been made, for often colloid is present in some but not in all sections, and it is unusual for it to be completely absent except in infancy.

Though the presence of colloid is not to be interpreted as pathological, the larger cystic collections cannot be regarded as strictly normal, seeing that the secretion should drain freely by the lymphatics. This method of drainage is primitive compared to that in duct-provided glands, and obstruction to the flow is more likely when the freedom of exit depends on lymphatic spaces and capillaries. The tenaciousness of colloid adds another difficulty, and cystic collections are to be accounted for on these grounds. A strictly analogous condition is seen in the formation of cystic adenomata in the thyroid gland.

Parathyroid cysts are usually contained in spaces lined by the regular pavement endothelium that occurs in lymph-capillaries, and though it is probable that the spaces represent distended lymph-vessels, it is possible that a few of them are over-distended parathyroid vesicles, the lining cells of which have become flattened by pressure. It may be mentioned that in the parathyroids of certain animals cysts have been described with a lining of ciliated epithelium. Thus Lusena has recorded the presence in canine parathyroids of cysts lined by epithelium with long, well-preserved ciliae. Edmunds illustrated a vesicle with ciliated epithelium from a dog's parathyroid. On the other hand, non-ciliated cysts have been observed in the sheep by Schaper, in the dog by Kohn, in the cat by Kohn and by Nicolas, in the rabbit by Nicolas, and in the kinkajou by myself. I have never met with ciliated epithelium in the parathyroids of man or animals, but have occasionally noticed

a condition which at first sight suggests ciliae arising from the parathyroid cells. This occurs when a mass of colloid has shrunk away from the enveloping epithelium but has left numerous delicate filaments passing to the cells. The nature of these filaments is readily ascertained under a high power, and the appearance is related to the factitious scolloping of the surface of the colloid that is often seen both in the thyroid and the parathyroid.

Fatty changes. These occur in two forms, first as intracellular fat, and secondly as fatty infiltrations of the glands, or interstitial fat.

(*a*) *Intracellular fat.* The first recognition of intracellular fat appears to have been made by Benjamins, who mentions fatty degeneration as one of the changes in the parathyroid cells. Erdheim studied its nature more fully, and showed that some of the granules found in the protoplasm were soluble in ether-alcohol, stained with scharlach, and gave the alcohol-osmium reaction. According to this observer, the fat appears within the first few months of life as minute drops and increases in quantity up to old age, by which period the drops are often doubly as large as the nuclei. The fat-content of the epithelial cells is dependent on age, but scarcely at all on the nutrition of the individual. Oxyphile cells are always strikingly deficient in fat. Petersen, staining his specimens with osmic acid or sudan, found that small drops of fat were of frequent occurrence and were to be found at all ages of life. He regarded their presence as physiological. Recently, Harnett has confirmed these observations, and has noted that fat may occur in cells at all stages of activity and rest. He could not satisfy himself that it was present in greater amount in discharged than in resting cells, though he inclined to think that this distinction held, and he concluded, like Petersen, that the fat is related to the functional activity of the gland.

(*b*) *Interstitial fat.* Fat spaces form a prominent histological feature of many glands, and were described by Sandström in his original paper. This fat is not an invariable content, and, as has been noted by Petersen, Harnett, and myself, is usually absent in infancy. It occurs as a few isolated cells, or the greater part of the gland may be occupied by fat, whereby the cells are broken up into widely separated clumps. Erdheim dates its first appearance from the fifth year, and states that it progressively increases with age until in old people its total amount exceeds that of the parathyroid proper, though it depends on the state of nutrition of the individual. This fatty infiltration has been interpreted by most observers as a normal feature of the glands. Berkeley, Petersen, and Shattock attached no special significance to its presence, and Welsh regarded it as normal, at any rate when not present in excess. Harnett, however, believes that this fat is contained in worn-out parathyroid glandular cells, that is, that it represents a degenerative change in the parenchymatous elements. Humphry inclines to regard the condition as pathological, and suggests that fatty infiltration is a feature of the parathyroids in exophthalmic goitre.

My own experience has been that interstitial fat is not only of very frequent occurrence, but that it is not related to any special disease or group of diseases.

In the present series it occurred to considerable amount in, e.g., cases of cancer, granular kidney, tuberculous meningitis, diabetes, rheumatic endocarditis, cirrhosis of the liver, cerebellar abscess. Even when present in greatest quantity it was not associated with any atrophied or degenerated condition of the parathyroid cells or vessels. Harnett regards the intracellular and interstitial fat as two stages in the same process, but he does not appear to have traced the intermediate stages, which on his hypothesis should exist, between the 'minute droplets of fat in the cytoplasm' and the cells fully distended with fat. Of the latter he says that they differ 'in no way from fatty tissue as met with elsewhere in the body'. Petersen recognized both forms of fat, but does not suggest that the interstitial form is distinct from ordinary adipose tissue, and both he and Harnett mention that it may be absent when the intracellular form is present, and Harnett has observed the converse. As has been mentioned, Erdheim found that the first appearances of the two varieties were not synchronous, and that while interstitial fat was dependent on the general nutrition of the individual, intracellular fat bore no such relation. Welsh frequently met with a lobule of fat at one end of a parathyroid, both being enclosed in the same capsule, and this observation I can confirm. One parathyroid from the present series points to the identity of interstitial fat and ordinary adipose tissue. It was taken from a somewhat obese woman of 48, having been found embedded in fat below the inferior pole of the thyroid gland. Sections showed that at one place, where a dimpling of the surface suggested a hilum, the surrounding fatty tissue could be seen to be directly continuous with the fat which was present in considerable amount in the interior of the gland.

Until further evidence is obtained, showing that interstitial fat represents parathyroid cells in a state of extreme fatty degeneration, the probability that the fat spaces are comparable to the fat spaces found in other organs must be admitted. Their presence would therefore be normal in the parathyroid, just as it is in bone marrow. It is, however, present to greater amount in adult than in juvenile subjects, though this rule is not invariable, and I have found fat in quantity in the parathyroid of a girl of seven, and have noted its almost complete absence in many subjects over forty years. Further, it may be present in markedly different amounts in the various glands of the same subject.

II. The Condition of the Parathyroid Glands in Certain Diseases.

The condition of the glands has now been observed in about thirty different diseases. The particulars, which have never yet been collected, will be epitomized in the following pages, and to them will be added details of the examples in my own series. It will be convenient to group the diseases into three classes: (1) Diseases of the Ductless Glands (including blood diseases),

(2) Diseases of the Nervous System (i.e. diseases with symptoms which have been compared to those stated to follow parathyroidectomy), and (3) Other Diseases.

1. *Diseases of the ductless glands.*

A. Diseases of the Thyroid Gland,—Exophthalmic Goitre, Myxoedema, Cretinism, Parenchymatous Goitre.

B. Addison's Disease.
C. Diabetes.
D. Leukaemia.
E. Pernicious anaemia.

A. *Diseases of the thyroid gland.*

i. *Exophthalmic goitre.* Special interest attaches to the condition of the parathyroid glands in this disease, as its acuter forms have been attributed by some to a defective parathyroid secretion. The glands have been examined in this disease by MacCallum in nine cases, Humphry in four cases, Benjamins in three cases, Shattock and Harnett each in one case, and myself in one case—a total of nineteen cases.

MacCallum recorded his cases in two papers, in the first of which he stated that he had examined eight cases, but had found the glands in four only. This he attributed to the fact that three of his specimens had been removed by operation, and therefore the parathyroids may have been either left behind in the neck or lost from the specimen after removal. In another case, however, in which the thyroid was examined post mortem, no parathyroids at all were found. In the four remaining instances the glands were distinctly smaller than normal, in two there was no degenerative change except this decrease in size, but in the other two there were 'very distinct degenerative changes in the parenchymatous cells with overgrowth of connective tissue'. MacCallum thought it was 'justifiable to conclude that there was evidence in these cases of distinct diminution in the bulk, and degeneration and disappearance of the cells of the gland'. In a second paper the same observer recorded the condition of the parathyroids in nine cases, though it was not stated whether they were inclusive of any of those previously examined. In all nine the parathyroids were practically normal. In some instances a moderate atrophy of cells and induration or increase in the connective tissue was present, but the alterations did not seem to be constant or sufficiently extensive to support the idea that the parathyroids have anything to do with the development of exophthalmic goitre.

Humphry examined four cases. In the first only two parathyroids could be found even after the most careful search; in the second two were found, one being enclosed in the same capsule as an accessory thyroid gland. The number found in the third is not given, while in the fourth only one lobe of the thyroid removed by operation was examined, and to it one parathyroid was attached. In the first two examples all the parathyroids showed gross changes, consisting of extensive infiltration with fat. In the third case there

was less extensive infiltration and the gland cells appeared to be degenerating, while the fourth showed no infiltration, but the cells of the gland appeared to be undergoing change—the protoplasm was diminished, the nuclei large and crowded together.

Benjamins examined three cases of exophthalmic goitre, and in one of them found the parathyroid in a condition of diffuse sclerosis and the epithelium of the whole organ atrophied.

In Shattock's case and in Harnett's the glands presented no changes and the amount of fat was normal.

My own case was that of a girl of 20, in whom both lobes but not the isthmus of the thyroid gland were greatly enlarged. The weight of the entire gland was 220 grms. The structures in the neck anterior to the prevertebral muscles and deep to the sterno-mastoid muscles were removed *en bloc*, and every gland found on careful dissection retained for microscopical section. The thyroid gland, after fixing for twenty-four hours in formalin, was cut into thin slices, the cut surfaces scrutinized with a lens, and eleven different portions which suggested a possible parathyroid structure reserved for section. As a result, three parathyroid glands and two accessory thyroid glands were identified. Two of the parathyroids and one of the accessory thyroids were attached to lymphatic glands. Microscopically, the parathyroids differed from each other. The first was made up of the usual polyhedral cells arranged without definite formation, and contained a slight amount of interstitial fat. There were many oxyphile cells, and granular colloid could be found under $\frac{1}{12}$ in. objective. The second gland was similar as regards its cells, but contained a considerable amount of fat. In neither of these glands could anything definitely abnormal be recognized. The third gland, however, differed from both the former in that it contained numerous definitely formed vesicles, most of which were filled with colloid secretion, and some of which almost attained the size of an ordinary thyroid vesicle. Both the vesicle formation and the colloid were present to an unusual extent.

The accessory thyroids consisted of large vesicles lined by flattened epithelium and distended with copious colloid secretion. The lymphatic spaces between the vesicles were also distended with colloid. Intervesicular glandular tissue was absent.

The thyroid itself showed an excessive quantity of colloid and enormous vesicles lined by flattened epithelial cells. In many vesicles the lining membrane was folded to project into the lumina, and in other places there was marked epithelial proliferation, so that the cells lay four or five deep. Between the large vesicles frequently occurred very small vesicles and some fields showed only the small variety, but here as elsewhere there was colloid between the vesicles as well as in them.

ii. *Myxoedema.* The only account of the parathyroids in this disease appears to be that published by myself. In this case six parathyroids were found, two on the right side and four on the left. The glands showed a marked

tendency to vesicle formation, the lining cells being cubical, and colloid secretion was copious both in the vesicles and between the cells, while the lymphatics of the gland were distended with the same material, and on serial section were traced towards the surface uniting to form large channels which conveyed the secretion away from the gland. In addition there was some increase of the fibrous stroma, and in parts of the gland a delicate intercellular mesh was observed. These conditions are illustrated in the original paper. In addition to the parathyroids, two pale brown bodies were found below the left lobe of the thyroid gland, and microscopically they showed an advanced stage of fibrosis with some remains of glandular tissue and a few scattered drops of colloid. The fibrosis was less advanced than in the thyroid gland, more advanced than in the parathyroids, and sections might have passed for either degenerated accessory thyroid or parathyroid tissue.

iii. *Cretinism.* The first account of the parathyroids in cretinism was published by Maresch in 1898. In a post-mortem on a cretinous girl of 11 years the thyroid was completely wanting and no accessory thyroids were found. On each side of the larynx in front of the bifurcation of the carotid vessels, was a collection of fat in which, on serial section, were discovered two bodies—four in all. Maresch describes these in detail. Two—on each side—possessed the typical structure of a parathyroid and were enveloped in a connective tissue capsule : the length of one was six millimetres. The two remaining bodies were identified as parathyroids but showed unusual features, each being partly occupied by a large cystic cavity (5 mm. in diameter on one side) lined by flattened epithelium. The remains of the parathyroid tissue appeared as small glandular acini containing colloid.

Peucker in 1899 examined the body of a cretinous girl $2\frac{1}{2}$ years old. The thyroid was wanting and no accessory thyroids could be found. Two parathyroids, symmetrically placed, lay at the lower border of the cricoid cartilage 1 cm. from the middle line. In addition, a small fluctuating cyst, divided by a constriction into unequal halves, was discovered near the parathyroid on the left side under the sterno-hyoid and sterno-thyroid muscles. The right and left parathyroids measured 4·25 mm. × 2·5 cm. × 3·0 cm., and 4·2 cm. × 2·2 cm. × 4·0 cm. respectively, and the cyst was 8–10 mm. in diameter. This latter structure was lined by cubical cells and attached to one side of its wall was a mass of cubical glandular epithelium.

MacCallum and Fabyan in 1907 recorded the condition found in a female cretin of 13 years. No thyroid gland was found. Dissection exposed two fairly large parathyroids on the posterior wall of the pharynx and two lobulated, cystic bodies, one on each side at the level of the cricoid cartilage. The microscopical appearances were as follows. The two parathyroids were normal but contained no oxyphile cells or alveoli, though colloid was present. The cells were arranged more compactly than normal. The two cystic bodies were alike. They were made up of multiple cysts lined by flattened or cubical epithelium and containing granular colloid and desquamated and pigmented

cells. At one side of the cysts in each mass there was a little glandular tissue formed into acini with scarcely any lumen. 'There is no question', continue MacCallum and Fabyan, 'that this is thyroid tissue, although it does not resemble the normal very closely.' This interpretation will be discussed in the next section, but it may be mentioned here that the description of the cystic bodies suggests a parathyroid rather than a thyroid structure, and that in the centre of one cystic mass was embedded 'a small nodule of parathyroid tissue'.

iv. *Parenchymatous goitre.* Exclusive of his three cases of exophthalmic goitre already quoted, Benjamins examined seventeen examples of goitre. Of these, eight were colloid goitres, six parenchymatous, two proliferating, and one malignant. Unfortunately, the detailed condition of the parathyroids in each of these specimens is not given, but Benjamins briefly summarized their features by stating that none was of a size that could be regarded as excessive, many of them being small. Microscopically, no abnormal changes were to be seen.

Harnett examined post mortem a girl of 18, who died from tuberculous meningitis and in whom the thyroid was enlarged to double its size. The structure of the thyroid was normal, but many of its vesicles were much enlarged and colloid was abundant. The parathyroids showed a moderate amount of fat infiltration and large numbers of oxyphile cells. Colloid was present in considerable amount both in lumina and between the cells. Harnett adds that he had never seen as much colloid in any other case at the same period of life.

B. *Addison's Disease.*

The condition of the parathyroids in this disease has been recorded by Petersen, Humphry and Harnett. An additional case will be added from the present series.

Petersen briefly stated that colloid was present to an unusually large amount and had produced a cystic condition. This he regarded as abnormal and indicative of regressive changes. In Humphry's case the parathyroids appeared normal. Harnett noted a moderate amount of fat, both interstitial and intracellular, a few poorly developed oxyphile cells but no colloid. The thyroid itself was slightly fibrotic but showed abundance of colloid.

My own example was a man of 32. Two parathyroids and four accessory thyroids were found, and one of the parathyroids was associated with one of the accessory thyroids. In this example the two tissues were completely separated by a septum of connective tissue. Near the surface of the parathyroid, on the side remote from the accessory thyroid, the parathyroid tissue gave place to a small area of vesicular tissue resembling thyroid tissue and directly continuous with the parathyroid tissue proper. The latter contained no fat, but oxyphile cells and scattered drops of colloid were found. The other parathyroid was somewhat different in appearance. It was attached to a large mass of fibrous tissue, coarse septa of which passed into the gland. The clusters of parathyroid cells were distinctly isolated from those in adjacent compartments and there was apparent a striking attempt at concentric arrangements of cells, whereby in

some places a layer of cubical epithelium enclosed a central lumen containing colloid. There were plenty of oxyphile cells, singly and in clusters, and frequent collections of granular colloid between the cells. One large mass of homogeneous colloid near the surface of the gland was contained in a space lined by pavement epithelium.

The thyroid and accessory thyroids were normal and similar in structure. Both contained areas of interstitial cells without vesicles, but in the latter the follicles were for the most part smaller in diameter than in the thyroid.

C. *Diabetes.*

One case has been recorded by Petersen, one by Humphry, and five by Harnett. There are three additional cases from the present series.

Petersen's case was a child of 2½ years in whom the parathyroids showed an unusually great development of interstitial fat which was arranged as a network among the cell-strands. No further details are given. Humphry's case, a man of 60 years, showed well-marked fatty infiltration of the parathyroids. Of Harnett's five cases, the parathyroids of one, a woman of 37, were intensely congested, with scanty interstitial fat, a few oxyphile cells and no colloid. In the second case, a woman of 58, both intracellular and interstitial fat was present in large quantity, there were enormous numbers of oxyphile cells, many vesicles containing colloid, which secretion was present to enormous quantity: the thyroid was distinctly fibrosed. In the third case, a man of 25, the parathyroids were markedly congested, there was a moderate amount of both varieties of fat, a few oxyphile cells but no colloid. The fourth case, a man of 43, showed abundance of interstitial fat, a large amount of intracellular fat, slight congestion, abundant oxyphile cells, and a large amount of colloid in vesicles. Harnett's last case, a man of 42, disclosed marked congestion, an enormous quantity of both varieties of fat, a fair number of oxyphile cells and no colloid.

The three additional examples from the present series were all in women, their ages being 33, 48, and 53 respectively. (1) Four parathyroids, three being reddish in colour and associated with much fat, the fourth with the pale uniform appearance of a lymphatic gland. Two of the parathyroids were the largest met with in the series, one measuring 2·5 cm. by ·5 cm. by ·4 cm. With one of these latter a nodule of lymphatic tissue was associated. An accessory thyroid was found at the root of a pyramidal thyroid lobe which was present. One parathyroid contained much interstitial fat, a few oxyphile cells, no intercellular colloid, but two or three large spaces contained granular colloid. The second and third parathyroids resembled the first but had no spaces. The fourth parathyroid contained much fat and showed a distinct tendency to form vesicles. Near its surface were many small drops of colloid, and in the capsule a large collection of the same material in a lymphatic vessel. The thyroid gland, dark in colour, consisted of vesicles for the most part large, and many areas of interstitial cells (some of which were oxyphile) between

which were occasional drops of colloid. The accessory thyroid was normal. (2) Two parathyroids and one accessory thyroid were found. Both parathyroids contained much interstitial fat, many large and beautiful clumps of oxyphile cells with distinctly outlined granules were present in the protoplasm. Similar granules lay between the cells and also between the less oxyphile cells, There was one very large mass of colloid at the surface in a vessel lined by cubical epithelium. This colloid was homogeneous under $\frac{1}{6}$ inch objective, but granular under $\frac{1}{12}$ inch. The thyroid and accessory thyroid were as in previous case. (3) Cancer of the rectum was present in addition to diabetes. Two parathyroids were found on the right side but none on the left. Both showed a considerable number of fat spaces and oxyphile cells and a few vesicles with colloid. Two accessory thyroid glands were found. The thyroid itself weighed 41 grms. and part of its right lobe was occupied by a calcified cyst. The connective tissue of the gland was increased, vesicles were small, and there were many areas of interstitial cells. In one part an encapsuled area contained only minute vesicles enclosing colloid and a good many polyhedral cells between the vesicles. The accessory thyroids were very similar to the main gland.

D. *Leukaemia.*

Humphry examined one case and found that the parathyroids appeared normal. Harnett examined one case and recorded the glands as being very large and containing enormous quantities of both forms of fat. There were numerous oxyphile cells and a small quantity of colloid.

In one case in the present series (a boy of 4 years) no parathyroids were found. This result was perhaps accounted for by the very great number of enlarged lymphatic glands that lay in the neighbourhood of the thyroid, obscuring the normal structures. The thyroid was small for the patient's age, being no larger than in many infants.

E. *Pernicious anaemia.*

Petersen recorded the only instance of this disease, but contented himself with the single statement that the lower parathyroids showed almost complete cystic degeneration.

2. *Diseases of the nervous system with symptoms which have been compared to those stated to follow parathyroidectomy in animals.*

Owing to the fact that the symptoms stated to follow parathyroidectomy are chiefly nervous, a lesion of the parathyroid glands has been assumed to exist in eclampsia, paralysis agitans, tetany and epilepsy. The limited observations which have been made on the glands in these diseases will be considered, together with the condition of the bodies in bulbar paralysis and in chorea of pregnancy.

A. *Eclampsia.* Vassale quoted Pepere and Zanfrognini as having shown that in subjects dead of eclampsia there were either 'alterations' in the para-

thyroids or 'congenital absence' of one or two glands. Vassale omitted to give a reference to the original paper and I am therefore unable to amplify this brief quotation. Ewing examined the thyroids and parathyroids in some cases of eclampsia and found considerable variation in the amount of colloid present. It is not clear, however, whether this comment applies to the thyroid or to the parathyroids.

B. *Paralysis agitans.* Berkeley, acting on the suggestion of Luzzato and of Lundborg that paralysis agitans was the result of parathyroid disease, examined the glands in one fatal case. He found one parathyroid of less than average size on each side of the neck. Their blood-vessels were greatly thickened 'as elsewhere in all these patients', and the connective tissue was increased, constituting in places a true destructive cirrhosis. Other parts of the gland seemed normal. Berkeley was unconvinced that these changes bore any causative relation to the disease, and in suggesting the connexion explains that his hypothesis is merely 'a reaching out into the dark'. This single examination has not been confirmed by Thompson, who examined nine cases of paralysis agitans, in none of which did the parathyroids present any histological or other peculiarity that would serve to distinguish them from the parathyroids in individuals dying from other diseases.

C. *Epilepsy.* I have failed to find any account of the parathyroids in this disease. Alquier knew of no published account up to 1906.

D. *Infantile tetany and convulsions.* Humphry examined a case of convulsions (? infantile) and the parathyroids appeared normal. Harnett obtained the glands from a boy of three years who died of tetany and diarrhoea twelve hours after food-poisoning, and found them markedly congested, with minute traces of fat, both interstitial and intracellular, visible only with a $\frac{1}{12}$ inch objective, a trace of granularity in some cells and no colloid. Thompson found no changes in the parathyroids of the only case of infantile convulsions he examined.

In the present series two cases were examined. A child of three months who died of 'infantile convulsions—exhaustion' showed the usual type of infantile parathyroids with complete absence of all signs of activity (oxyphile cells, granularity of protoplasm, colloid). The glands were congested to a slight extent, and one of them was composed at one extremity of fat alone. The second infant died with tetany, and post mortem presented three parathyroid glands, all of which were typically infantile in character and showed no morbid change. No accessory thyroids were found and the thyroid gland itself was normal.

E. *Bulbar paralysis.* Humphry examined one case and recorded the glands as appearing normal.

F. *Chorea of pregnancy.* No previous case has been recorded. One example in present series occurred in a woman of 20. Two parathyroids only were found and no accessory thyroids. The parathyroids were intensely congested, but there was no change in the cells, many of which were oxyphile. One gland, more active than the other, showed at the surface a large mass of

colloid contained in a vessel lined by cubical epithelium. Interstitial fat was absent. Many of the lymphatic glands examined were occupied by extensive haemorrhages, which were perhaps the result of the severe convulsions that occurred before death. This explanation would be sufficient to account for parathyroid congestion. The thyroid gland was normal.

3. *Other diseases.*

There are a few diseases in which the parathyroids have been examined, although no morbid function of the glands had been suspected; these may be conveniently grouped together. Details have been published of the parathyroids in acute nephritis, tuberculous disease, pneumonia, broncho-pneumonia, bronchiectasis, septicaemia, scarlet fever, diphtheria, pertussis, marasmus, acute yellow atrophy, carcinoma, and sarcoma. These will be briefly summarized, together with additional examples from the present series, and the section will be concluded by an account of the glands in cases of chronic interstitial nephritis, typhoid, infective endocarditis, simple rheumatic endocarditis, cirrhosis of the liver, rachitis, and infantile diarrhoea and vomiting.

Acute nephritis. Harnett described the parathyroids in a case of Vincent's angina with acute nephritis (boy, aged 4) as being devoid of interstitial fat, oxyphile cells and colloid. In one case of the present series, a girl of 10, with acute nephritis, one parathyroid and four accessory thyroids were found. The parathyroid showed no interstitial fat, a few oxyphile cells chiefly in cortical regions, no drops of colloid. The thyroid was normal.

Tuberculous disease. Humphry examined a case of 'tubercle' and found the parathyroids normal. Harnett investigated five cases. A man of 26, with phthisis and alcoholic neuritis, showed parathyroids with much interstitial fat, a few oxyphile cells, and some vesicles containing colloid. Of two children, aged 10 and 14 respectively, with tuberculous peritonitis, the parathyroids of the former contained much interstitial fat, a slight fatty change in the cells, a few scattered oxyphile cells, and no colloid; the glands of the latter, who had also hip disease with lardaceous liver and spleen, showed marked fatty change, slight fibrosis and thickening of the capillary walls, some of which were lardaceous. A girl of 3, with general tuberculosis, had parathyroids without colloid or fat, and most of the cells were without granules. The fifth case (tuberculous meningitis) was that already mentioned as having a parenchymatous goitre. Carnot and Delion's specimen has already been quoted, as well as Benjamin's case of miliary tuberculosis.

Five of the present series died of tuberculous disease. i. Girl of 7 months, with tuberculous mediastinal glands, caseous pneumonia, tuberculous ulceration of intestines. Eleven parathyroids were present and no accessory thyroids. The parathyroids all showed infantile characters with clear protoplasm and no fat, but two of them showed in places slight signs of activity, and one of these contained a drop of colloid. The thyroid gland contained between the vesicles interstitial glandular cells, among which were drops of colloid.

ii. Male, 3½ years, with general tuberculosis. The five parathyroids were all infantile, with no colloid or interstitial fat, but a few slightly granular cells were seen. The thyroid was normal. No accessory thyroids were found.

iii. Female, aged 7 years, with caseous mediastinal glands and tuberculous meningitis. Four parathyroids, all infantile were found. There were a few cells with granular protoplasm, and no vesicles. One of the parathyroids was attached to a lymphatic gland and contained many oxyphile cells. The thyroid was normal. No accessory thyroids were found.

iv. Female, aged 28, with phthisis. The parathyroids were congested and showed many moderately granular cells; no vesicles, colloid, or interstitial fat were present. The thyroid with connective tissue stroma was increased and very few interstitial cells were seen.

v. Male, aged 45, with phthisis. The majority of the cells were faintly granular, but typical oxyphiles present. Marked tendency to form vesicles, especially at the surface, where regular acini were found. Small drops of colloid were scattered between the cells, and near the surface was a large lymphatic filled with colloid. The connective tissue was slightly fibrosed. Much colloid was found in lymphatic spaces, as well as in vesicles. Many of the latter contained, in place of colloid, large clumps of polyhedral cells, and many similar cells lay between the vesicles.

Pneumonia. In one case the parathyroids were noted by Humphry as normal.

Broncho-pneumonia. Harnett's three cases were as follows: i. The parathyroids were without fat or colloid, the cells were clear, but here and there traces of oxyphile granules were seen. The thyroid contained no colloid.

ii. Female of 9 months: following pertussis. Parathyroids with extensive haemorrhages were found, no fat or colloid, but traces of oxyphile cells were seen. The thyroid contained no colloid.

iii. Male of 16 months. Parathyroids of the usual infantile type were present. They were slightly congested and showed traces of granulation in some cells.

In the present series there were four cases. The parathyroids for the most part were infantile, but two showed small amounts of interstitial fat; two showed slight granularity of protoplasm, and one (a boy of 11 months), occasional drops of colloid. All the parathyroids of each subject were not necessarily alike, either as regards oxyphile granules, colloid, or fat.

Bronchiectasis. One case by Harnett (a male of 12 years) had parathyroids with a small amount of fat which was wholly intracellular, a few oxyphile cells were seen but no colloid.

Septic conditions. A boy of 2 days, with ruptured spina bifida, sepsis, and suppurative meningitis (Harnett), had parathyroids of the usual infantile type, but there was intense congestion and here and there haemorrhages.

Two cases in present series. i. Infant, with sloughing of penis and septicaemia following paraphymosis. Parathyroids of the infantile type were found,

but the cells showed hyaline degeneration. ii. Girl of 7 years, with otitis media and cerebellar abscess. The parathyroids had a fair number of fat spaces and oxyphile cells. Some drops of colloid, especially near the surface, were seen.

Scarlatina, diphtheria, pertussis. Garnier states that in some examples of these diseases the parathyroid cells presented an atrophied appearance as though exhausted by too abundant secretion. Lesions in these cases were more frequent in the thyroid than parathyroids. Harnett's case of pertussis has already been mentioned.

Marasmus. Five cases examined by Harnet. i. and ii. The cells were all very translucent with non-staining protoplasm, no oxyphile granules or fat were seen. iii. Faint traces of granularity were present in the cells, no colloid, fat, or oxyphile cells. iv. Typically infantile except for very faint traces of granularity. v. Infantile type.

Thomson records the findings in twelve cases of primary infantile atrophy. The parathyroids are stated to have shown changes which were progressively degenerative in type, but a similar condition was present in the thymus and other ductless glands.

In the present series was one case—a boy of 11 months. The parathyroids were only partially infantile in type, most of the cells showing faintly granular protoplasm. There was a small amount of interstitial fat and occasional drops of colloid.

Acute yellow atrophy. Ewing, in a discussion following his paper already quoted, stated that he had found 'some remarkable changes' in the parathyroids in acute yellow atrophy, but no further details are given except that the changes were not uniform.

Malignant disease.

1. *Carcinoma.* In one case Humphry found the parathyroids normal. Harnett examined five cases. i. Primary cancer of cirrhotic liver. Male, 44 years. A fair amount of interstitial fat was present, much intracellular fat, large masses of oxyphile cells and much colloid. The thyroid was congested with active proliferation of cells, marked fatty changes were present in those lining the vesicles, very little colloid was found: in parts it resembled an adenoma.

ii. Cancer of pylorus in a female of 28 years. Intracellular fat was marked, all the cells were more or less oxyphile, there was a very small amount of colloid: it was an active gland.

iii. Cancer of stomach in a male, aged 63 years. Thickened septa were seen but no definite intercellular fibrosis, large numbers of oxyphile cells, traces of colloid, enormous quantity of fat, both intracellular and interstitial, were found. The thyroid showed marked fibrosis and a fair amount of colloid.

iv. Cancer of stomach in a male of 44 years. A moderate amount of interstitial fat and an enormous quantity of intracellular fat were present, oxyphiles were abundant but no colloid.

v. Cancer of prostate in a male of 67 years. The parathyroids were rather

large, a fair amount of interstitial fat, large numbers of oxyphile cells but no colloid was present.

In the present series were four cases. i. Cancer of colon in a female of 60 years. A large amount of interstitial fat, many oxyphile cells, and small drops of colloid, especially among the oxyphile cells were present; a large lymphatic vessel containing colloid was near the surface. In the thyroid the connective tissue septa were thickened.

ii. Cancer of prostate in a male of unknown age. A small amount of interstitial fat was present (one parathyroid had a large amount). Many oxyphile cells, numerous drops of colloid, many lymphatic vessels containing colloid were seen, one being visible to the naked eye. The thyroid was normal.

iii. Cancer of the rectum in a male of 58 years. A very small amount of interstitial fat, a very large number of oxyphile cells, single and grouped were seen, no drops of colloid were found, but in intercellular spaces were many collections of oxyphile granules. The thyroid contained three encapsuled, opaque, white bodies made up of vesicles which were all minute, in marked contrast to remainder of gland in which were numerous large vesicles.

iv. Cancer of rectum and diabetes in a female of 53 years. The details of this case have already been given (p. 301).

2. *Sarcoma.* In the parathyroids of a man of 43 years, with sarcomatosis, Harnett found scattered single oxyphile cells, no colloid, and scanty interstitial fat.

In the present series were three cases. i. Mediastinal sarcoma in a female of 43 years. No parathyroids were found. The thyroid was markedly enlarged and contained a large cyst with thick calcified walls. Microscopically, there was very active secretion of colloid, many lymphatic spaces being widely distended with the secretion.

ii. Mediastinal sarcoma in a male of 64 years. No interstitial fat but many oxyphile cells and an occasional drop of colloid were seen. One of the parathyroids showed a distinct tendency for its cells to form vesicles, and there occurred, especially near the surface, a greater amount of colloid than in the other glands. The thyroid contained a considerable amount of intervesicular glandular tissue with drops of colloid.

iii. Cerebral tumour in a male of 45 years. One lobe of the thyroid contained three encapsuled, translucent, white bodies the size of peas, which, microscopically, were parathyroids with many oxyphile cells, some colloid, but no interstitial fat. The thyroid contained a fair amount of intercellular glandular tissue.

There remain some half-dozen diseases in which the parathyroids have not been described by previous observers, but of which specimens were examined in the present series.

1. *Chronic interstitial nephritis.* Four cases.

i. Male, 61 years. In the parathyroid was no interstitial fat, many oxyphile cells and a few drops of colloid. The connective tissue was not increased.

ii. Male, 71 years. No interstitial fat was found in the parathyroids, large numbers of oxyphile cells, but no drops of colloid were seen.

iii. Male, 52 years. The parathyroids were black in colour to the naked eye. Slight fibrosis was present. There was no interstitial fat, a few oxyphile cells and drops of colloid were present. The thyroid had large numbers of intervesicular cells, some being oxyphile and others arranged to form minute vesicles.

iv. Male, 47 years. There was slight general fibrosis of the parathyroids, a considerable amount of interstitial fat, a few oxyphile cells and no colloid.

It will be remembered that MacCallum's parathyroid tumour occurred in a case of chronic nephritis.

2. *Typhoid.* Male of 17 years. A few fat-spaces were seen in the parathyroid. The majority of the cells appeared to have undergone hyaline degeneration.

3. *Infective endocarditis.* Female, 26 years. There was no interstitial fat, a fair number of isolated oxyphile cells but none in clusters, drops of colloid and at surface regular vesicles enclosing colloid.

4. *Rheumatic endocarditis and pericarditis.* Female, 8 years. There was a fair amount of interstitial fat, a few cells with slightly granular protoplasm. One gland contained a haemorrhage.

5. *Cirrhosis of liver.* Female, 50 years. There was an excessive amount of interstitial fat, many oxyphile cells, drops of colloid, some being in vesicles, and on the capsule of one gland a lymphatic containing colloid.

6. *Rachitis.* Male, ? 2 years. The parathyroids showed a few fat-spaces, but otherwise were typically infantile.

7. *Diarrhoea and vomiting.* Male of 3 months. No fat or colloid but a few oxyphile cells were seen.

III. The Rôle of the Parathyroids in Disease.

The foregoing sections will have shown that, though pathological changes in the parathyroids are fairly common, they may occur without producing any clinical symptoms resembling those ascribed to parathyroid ablation in animals. The observations recorded tend rather to suggest that the bodies play but little part even in those diseases with which they have been most freely associated by many writers. The belief of Pepere and Zanfrognini, that the absence of one or two parathyroids is responsible for the occurrence of eclampsia, is hardly tenable; first, because the same numerical deficiency may be found in parous women who have not been the subjects of these convulsions, and secondly, because the physiological principle governing hypertrophy would lead to an increase in size of such parathyroids as were present, and thus a deficiency of the secretion would be obviated.

The only instance of a lesion of a parathyroid having been directly associated with definite symptoms in life, is that recorded by Carnot and

Delion, who found post mortem one tuberculous parathyroid in a woman who had died of phthisis of many years' standing. She had suffered for the eight hours preceding death from convulsions which these authors ascribe to parathyroid insufficiency. Before accepting this conclusion, it must be remembered that two other non-tuberculous parathyroids were discovered, which, though sclerosed, were made up of healthy cells; that in addition to advanced tuberculous disease of the lungs there was a pneumothorax and fatty degeneration of the liver and pancreas, that the kidneys were not healthy ('les reins sont relativement très peu touchés'), and that there was considerable oedema of the meninges. Caution is obviously necessary in interpreting these agonal convulsions as evidence of parathyroid disease.

Although no constant lesion of the glands has been found in any disease, it may be noted that a striking feature of most of those examined in diabetes has been the presence of much fat. In one case it was scanty, and in a second moderate, but in the remaining eight cases fat was particularly abundant. Additional observations must decide whether this feature is merely coincidental, or is comparable to the fatty changes that appear in other organs (e.g. the liver and kidneys) in diabetes, or bears a more intimate relation to the pathogeny of the disease.

Among the examples which indicate that changes in the glands occur without entailing any interference with health and without complicating existing disease, are the so-called parathyroid tumours. Their histological structure leaves it open to question whether the specimens were not merely abnormally enlarged examples of a gland known to vary much in size, and in this event the term 'tumour' implies more than the condition deserves, and 'hypertrophy' would probably be a more exact expression. In none of them was there any clinical condition to account for the increase in size, and in none did the growth result in any but local symptoms, while in three out of five instances the enlarged gland was encountered unexpectedly in course of post-mortem examination.

The cases which would be most likely to disclose the effects of parathyroid insufficiency are those in which the glands have been found in a condition of degeneration, but in no instance, with the exception of Carnot and Delion's case already referred to, was there any suggestion that the clinical condition depended on the diseased organs.

The causative relation between the parathyroids and eclampsia, paralysis agitans, tetany or epilepsy is not at present founded on pathological observations. The limited evidence at our disposal goes to show that in the three first-named the parathyroids are unchanged, while their importance in the production of epilepsy is not based on post-mortem examination.

As regards the various diseases of the thyroid gland, much importance has been attached to the possibility of healthy parathyroid tissue being associated with a diseased thyroid. The combination has been observed more than once and has been held by MacCallum, Fabyan and others to prove the functional independence of the two tissues. Further support for this view

has been claimed from the fact that in three cases of thyroid insufficiency (cretinism) the parathyroids have failed to become transformed into thyroid tissue. These two points are of sufficient importance to deserve further consideration.

The records of the only three cases of cretinism in which the parathyroids were examined show that some of these glands remained normal, but others had undergone definite change. In MacCallum and Fabyan's recent example there were two parathyroids, symmetrically placed and apparently healthy, and also two cystic bodies, one on each side of the neck. These latter the authors regarded as accessory thyroids, though they admit that their structure bore no very close resemblance to normal thyroid tissue, and that it differed histologically from a nodule of accessory thyroid tissue found at the root of the tongue. It has been pointed out earlier, that the description and illustration of these bodies suggest rather a parathyroid than a thyroid origin. In each was a mass of glandular tissue formed into acini which had scarcely any lumina, and the tissue as figured lacks the features of a normal thyroid —vesicles, with a cubical or columnar epithelial lining and colloid contents—but possesses the usual features of a parathyroid—polyhedral glandular cells, some irregularly arranged, others showing a tendency to regular setting round a central cavity, others again grouped quite regularly round a central acinus. The additional fact that the left cystic body contained in its centre a nodule of undoubted parathyroid tissue, strongly confirms the view that these two cysts were really degenerated parathyroids. In Maresch's case, four parathyroids were found and two of them were cystic. In Peucker's example, two parathyroids were discovered, and in addition a cyst. This was lined by cubical epithelium and filled by a coagulated material of mucous character. In connexion with it were masses of glandular cells, and Peucker inclined to regard the body as a parathyroid.

In each of these cases there appear to have been changes in one or more parathyroids, and it will have been observed that in two of them only a couple of parathyroids were found, although four is the number most frequently present. So far as this limited series goes, it cannot be affirmed that the parathyroids are not affected in cretinism, though their degeneration may be delayed beyond the time when the thyroid has atrophied. On the other hand, it may seem that the persistence of some parathyroids, even when the thyroid is completely degenerated, is not easy of explanation. MacCallum and Fabyan's case, in which a nodule of actively functioning thyroid tissue was found at the root of the tongue, proves, however, that accessory thyroid tissue can exist with complete atrophy of the thyroid gland, and therefore the presence of healthy parathyroids in cretinism is not incompatible with the hypothesis that they are thyroidal in nature. As bearing on this point, it may be observed that the majority of cretins possess thyroids which contain functional gland tissue (Berry).

The second point—the failure of the parathyroids to undergo conversion to thyroid tissue when the latter is deficient—has been quite commonly held to indicate the functional independence of the two structures. The question,

however, may be asked, Why should the parathyroids become thus converted? They normally secrete colloid, even in considerable quantity, without assuming a thyroid structure, and often remain unconverted in old age. It must be recognized that the change undergone by the embryonic thyroid, whereby vesicles are formed, clearly leads to the gland becoming a capacious reservoir of colloid, whereas the parathyroids turn out their secretion into the lymphatic stream as soon as it is formed. The additional demand for parathyroid colloid, consequent on thyroid atrophy, would hardly result in the parathyroids developing into reservoirs for storing the very secretion which is in urgent demand elsewhere, and the chief factor in the formation of vesicles—a collection of colloid—would not arise and the parathyroid structure would persist.[1]

As regards the glands in exophthalmic goitre, they have been found unaltered in some cases, in others degenerated (MacCallum), atrophied (Benjamins), or in a condition of increased activity (Forsyth). The numbers present in different cases vary, and in one subject none was found (MacCallum).

In conclusion it must be admitted, that observations on the morbid states of the parathyroids are not yet sufficiently numerous or concordant to justify the opinion that the glands bear a pathogenic relationship to any known disease. Their condition in the several affections of the thyroid gland is variable, and further research is needed in this direction.

The value of future investigations would be enhanced by observance of certain precautions which have received less attention than they merit. In the first place, the difficulty with which parathyroids are identified by the naked eye calls for minute dissection and microscopical examination of all glands discovered, while the existence of structural variations in the parathyroids from the same subject makes it necessary to withhold an opinion on their condition until each has been examined. Their histology should be studied in many sections, for colloid, oxyphile cells, vesicles, and fat are not equally distributed through all parts. In every case of thyroid disease, the accessory thyroids should be enumerated and their microscopical features studied, and finally, peculiarities in structure of the thyroid itself should be sought by cutting its lobes into thin slices and sectioning all suspicious areas. These precautions, though rendering the work more laborious, will furnish more exact results than those obtained by less detailed investigations.

[1] This conception of the thyroid gland as a reservoir of colloid emphasizes a distinction between this and other ductless glands such as the pituitary and adrenal, in which collections of secretion are formed, if at all, only to very limited amount. The point bears on the therapeutic employment of these glandular tissues. Extracts of thyroid gland contain much colloid and are successful remedies in thyroid deficiency; extracts of pituitary and of adrenal glands can contain but little of their respective secretions, and are of comparatively little service in the treatment of those diseases in which, by analogy to myxoedema and cretinism, they should be curative. The administration of very much larger doses of pituitary and adrenal extracts seems to be justified on histological grounds, and I hope to have an early opportunity of putting this modified method of treatment into practice.

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PERSISTENT HEREDITARY OEDEMA OF THE LEGS WITH ACUTE EXACERBATIONS. MILROY'S DISEASE

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With Plates 34 and 35.

The case which has led us to write this paper is as follows:—

Alice Wherrell, aged 18, was sent up to Guy's Hospital in 1906, having been under observation at Caversham for seven years previously. Her family history is remarkable; it is given a place to itself later in the paper. The patient was quite normal looking when born, but in 1888, when three months old, she was noticed to have swollen feet, and apparently there was no cause for the swelling. It was recognized by the parents as being the beginning of the family complaint. The child grew up in the usual way, and there is no clear history of how the 'oedema' spread; but it is definitely stated that the swelling, though varying in amount from time to time, never went quite away, and it slowly became more persistent and extensive. By 1899, when she was eleven years old, both legs, from knees to toes, were so swollen that she had to wear bandages. The latter kept the swelling down to some extent; without bandages the legs became enormous. Her only other trouble was a chronic inflammation of the eyelids, dating from birth. The general health was not interfered with, and when the legs were bandaged she could get about quite well. At no time was there oedema elsewhere than in the legs. There was no breathlessness, no tendency to chilblains, no gastro-intestinal disorder sufficient to attract attention, no suggestion of Raynaud's phenomena, no urticaria, indeed nothing but apparently causeless firm swelling of the legs of the nature of semi-solid oedema. This affection being common in the family, little attention was paid to it; and when, in August, 1900, she first saw Dr. Hope it was not on account of her legs, but of her eyes—an exacerbation of the blepharitis which she had had all her life. Ophthalmoscopic examination showed healthy optic disks and retinae; both ocular and palpebral conjunctivae were injected from an acute conjunctivitis which had recently developed upon a chronic blepharitis. Vision was $\frac{6}{18}$ in each eye, and there was slight photophobia. The acute conjunctivitis was soon

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relieved, though the chronic blepharitis persisted as before. It seemed that the conjunctival condition was, in a sense, accidental, and not directly connected with the swelling of the legs. The latter had the appearance of moderate elephantiasis, similar to, but less in degree than, their condition in 1906. They remained in much the same state from 1899 to 1904, and then occurred the first of a series of 'acute attacks' of pain and additional swelling.

We propose to give a somewhat detailed account of these 'acute attacks', because they have not occurred, or, at least, they have not been prominent features, in the similar cases of hereditary trophoedema recorded by Milroy, Meige, Rolleston, and others.

The first 'acute attack' occurred on January 19, 1904. The patient at first noticed an acute pain in her pudenda, but did not regard it as serious. The next day she walked to a neighbouring town, and this made the pain in the pudenda so much worse that she had much difficulty in walking back again. When she got home she went to bed. Her temperature was only 97·4° F., and her pulse rate 74 per minute, but she was shivering in spite of hot-water bottles in the bed. The pudenda were generally swollen and painful, especially the left labium minus, and there was a red patch over the metatarso-phalangeal joint of the right great toe. The swelling of the legs was not materially increased at the time, and the local condition gradually improved until, by January 26, she had practically recovered from the acute attack, the pudenda had become normal again, pain was gone, and the legs were as before—chronically swollen from the knees downwards.

This was the only occasion on which the pudenda have been affected at all, and also the only occasion on which there was no rise of temperature during one of these acute attacks.

The second 'acute attack' began on June 10, 1904. At 6 a.m. the patient had a severe fit of shivering which lasted an hour and a half. She then vomited four times at short intervals, after which she became very hot and experienced severe continuous pain down her right thigh and leg, from Poupart's ligament to the ankle. Her temperature was 104° F., her pulse rate 126, and her respiration rate 52, per minute. The right thigh, leg, and foot, beginning sharply at Poupart's ligament, were red, enormously swollen, very hot to the touch, painful, and so tender that any pressure that could be borne failed to cause any pitting. The left thigh and leg felt hot also, but they were neither red nor painful, and the swelling on the left side was only the same as had been present for years. The measurements taken at the time showed:—

Maximum circumference measurements.

	Right side.	Left side.
Instep	13 inches.	12 inches.
Calf	$16\frac{5}{8}$ „	$17\frac{1}{4}$ „
Knee	$21\frac{5}{8}$ „	$21\frac{1}{8}$ „
Thigh	$23\frac{1}{3}$ „	$24\frac{1}{4}$ „

We have no record of measurements previously to this, but clinically the left leg had always been considerably more bulky than the right hitherto.

There were no abnormal physical signs in the lungs nor in the abdominal organs. The only abnormal physical sign noted in the heart was a faint blowing systolic murmur, which was heard both at the impulse and at the base; it was thought not to indicate any valvular disease.

Next day, June 11, 1904, the temperature had fallen to 100° F., the pulse rate to 106, the respiration rate to 40. The right lower limb was still hotter than the left, the redness above the knee had disappeared, and that below the knee was fading markedly. Pain was also much less.

On June 12, 1904, the systolic bruits were scarcely to be detected. The temperature was 99° F., the pulse rate 100, and the respiration rate 20 per minute. The right lower limb was desquamating, and the pain in it was almost gone.

By June 16, 1904, the attack was quite over, the temperature was 98° F., the pulse rate 60, and the respiration rate 20 per minute.

Measurements showed:—

Maximum circumference measurements.

	Right leg.	Left leg.
Instep	11½ inches.	10½ inches.
Calf	14¼ „	14¼ „
Knee	17 „	16½ „
Thigh	21 „	21½ „

Both legs had diminished in size, as was always the case, to some extent, when the patient lay in bed for a week.

The third 'acute attack' occurred on Aug. 22, 1904, and was very similar to the second. It may be noted that up to this time there had been no breach of surface in either leg, no boil nor sore place that could be detected, and no enlarged lymphatic glands in the groins or elsewhere. The urine had a specific gravity of 1010; it was pale and clear, with a neutral reaction, and it contained neither albumen nor sugar.

The first breach of surface that was noticed was some time after the patient had been up and about after recovery from the third 'acute attack'; on Nov. 1, 1904, there were numerous small superficial ulcers in the skin about both knees. These ulcers were mostly no more than an eighth of an inch in circumference, the largest measuring half an inch across; each had a sloughy base, an indefinite edge, and a thin serous discharge, which was small in amount. Each excoriation was surrounded by an area of redness due to inflammation. There was nothing suggestive of syphilis in the appearance of the very shallow sore places; they seemed to be pyodermic from accidental infection of the poorly nourished skin.

The fourth 'acute attack'. On Nov. 4, 1904, about 3 p.m., the patient complained of shivering, and of severe pain down her left side. Half an hour

later both lower limbs became hot and began to swell. A typical attack followed, like the previous ones in every respect, except that both legs were affected equally instead of one more than the other.

The fifth, sixth, seventh, eighth, ninth, and tenth 'acute attacks'. These occurred at intervals of a month or two during the year 1905. Each was confined to the right leg, was of short duration, and very similar to those already described. It is worthy of note that the patient was now eighteen years of age and had only menstruated once.

A short but acute attack of mental derangement occurred in February, 1906. On Feb. 19 of that year she became very excited and talkative, without apparent cause, and next day she was garrulous, with a happy, but unintelligent, facial expression, much exaltation, and delusions. The following day, Feb. 20, she was passing her motions and urine under her, and she had delusions about money. On Feb. 21 she was very noisy and persistently dirty in her habits. She continued in this abnormal mental condition throughout March, April, and May, but in June she gradually improved, and entirely regained her reason.

She was in Guy's Hospital from Nov. 1 to Dec. 1, 1906. The condition of her legs at that time is shown in the accompanying photographs (Figs. 1 and 2).

There was brawny, elephantiasis-like swelling of the whole of both lower extremities from Poupart's ligament and the gluteal fold above to the toes below. The pudenda were not affected, nor did the swelling extend on to the trunk. If any parts of the lower limbs were less affected than the rest, they were the plantar surfaces of the feet and toes themselves. The swelling appeared to be subcutaneous, the skin itself being dry, but only moderately thickened, and not discoloured. The swelling obliterated the normal outlines of the parts, bony prominences such as the malleoli, the patellae and the great trochanters not being made out. The swelling was comparatively uniform in the straight parts of each limb, with deep transverse sulci across the roots of the toes, in front of and behind the ankles, and behind the knees. On lightly handling the parts they felt almost hard, but on firmly pressing with the finger, for a longer time than is necessary in the case of ordinary oedema, deep pitting was obtainable, so that, even if there was a real increase in the subcutaneous connective tissues, there was considerable oedema as well, of the kind that is sometimes called semi-solid.

The legs were skiagraphed, and the X-rays showed no abnormality in the bones. It was impossible to examine the muscles digitally; they were certainly deficient in power, for the patient could stand with difficulty and could scarcely walk at all. It seemed likely, however, that this apparent weakness of the muscles might well be due to the mechanical difficulties in the way of their free action rather than to any real disease in the muscle fibres themselves. The electrical reactions were tested, but the resistance in the dry coarse skin was so great that no contraction was obtainable with any current, Faradic or galvanic, that the patient could bear over the quadriceps extensor femoris, or the ham-

string muscles of the legs. The tibialis anticus muscles responded to a bearable faradic current, and so did the long extensors of the toes and the muscles at the back of the calf, though the resultant movements of the toes or ankle were but slight. These muscles also gave a slight galvanic reaction, in which the kathodal closure contraction was more easily obtained than the anodal closure contraction. So far as could be judged, therefore, the electrical reactions were normal, though the difficulties in the way of obtaining them were great. The muscles of the upper extremities all gave a normal reaction with readiness.

As regards sensation, there was no abnormality. Cutaneous sensibility was present everywhere, and localization was correct. Heat and cold were properly distinguished, pain was felt distinct from touch, muscle sense was correct, and pressure sense was normal when allowance for the thickness of the superficial tissues was made. There was no cutaneous hyperaesthesia, and there was no pain at all. The feet themselves were not markedly colder than those of other patients in the wards at the same time.

The respiratory system was perfectly natural.

The alimentary system was apparently sound. The tongue was clean and moist, the teeth good, the appetite good; there was no tendency to nausea or vomiting, and the bowels were opened regularly. Neither liver nor spleen could be felt; indeed, no abnormality could be made out, and the abdominal wall was supple and natural right down to Poupart's ligament, where the swelling of the legs suddenly began.

The genital system was abnormal only in respect to menstruation, which had occurred but once, though the patient was 18.

The urine was also natural; its specific gravity was 1014, its colour pale yellow, its reaction acid; it was clear, of normal amount, and it contained no albumen, blood, pus, or sugar; microscopical examination showed no abnormal constituents. No excess of indican was present.

The temperature varied from 97° F. to 98·8° F., being for the most part slightly sub-normal. The pulse rate varied from 66 to 88, and the respiration rate from 20 to 24, per minute.

The heart appeared to be of normal size, and the sounds were clear and entirely free from bruit. The peripheral arteries that could be felt were natural; the maximum systolic blood pressure in the brachial artery, taken on many different occasions by Martin's modification of the Riva-Rocci apparatus, was never higher than 132 mm., and never lower than 120 mm. of mercury. There were no varicose or other distended veins to be seen anywhere, nor were there any telangiectases. The patient stated that her hands and feet readily became numbed and blue in cold weather, but no decided symptoms of Raynaud's disease could be found. The blood examination showed nothing distinctive. The red blood corpuscles numbered 4,120,000 per cub. mm., the leucocytes 8,437, and the haemoglobin was 80 % (male standard).

The differential leucocyte count was as follows :—

Polymorphonuclear cells	74 per cent.
Small lymphocytes	21 „ „
Large lymphocytes	3 „ „
Coarsely granular cosinophile corpuscles .	2 „ „

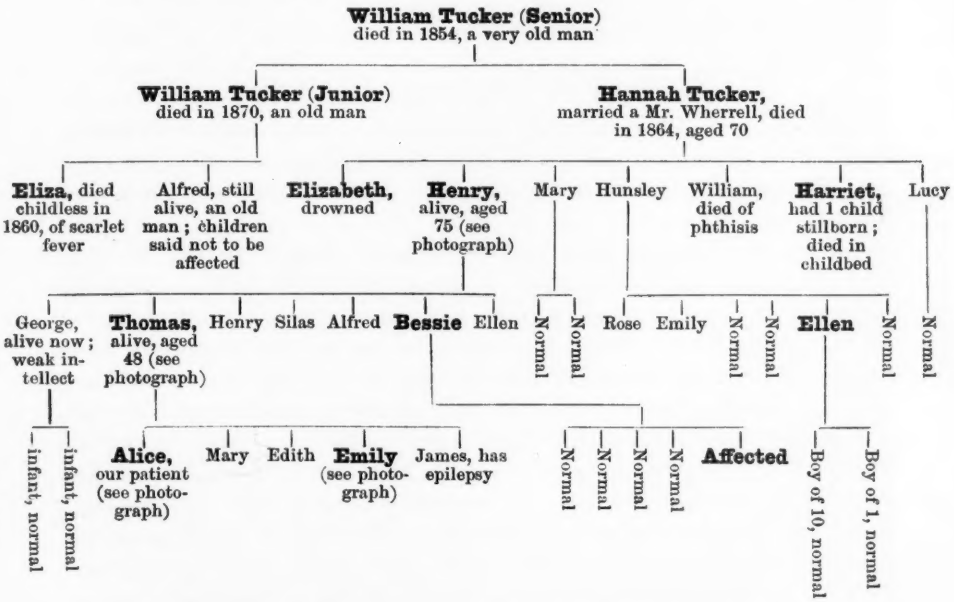
Filaria embryos were searched for in both night and day specimens of blood, and none were found. The patient, it may be mentioned, had not been out of England, so that filariasis seemed out of the question. The blood coagulation time was approximately normal.

The eye condition—chronic blepharitis and conjunctivitis—has already been alluded to.

The thyroid gland could be felt in the neck, and it seemed to be natural.

The patient's height was 5 ft. 3 ins.

Genealogical table of the family.



The individuals whose names are printed in thick type had, or have, the family complaint of 'swollen legs', mostly with 'acute attacks' as well.

The diagnosis of this patient's condition was much simplified when the family history was obtained. There were thirteen similar cases in five generations. When an individual had the hereditary complaint we summarize this by merely stating that there were 'swollen legs', without going into detail in each case. The swollen legs, when mentioned, began young and lasted long.

First Case traced.

GENERATION 1.—The first member of the family of whom we had any account was William Tucker. It is reported that he 'had very swollen legs all his life', but no further particulars are available. He died in 1854 at an advanced age.

Children of William Tucker, senr.

GENERATION 2.—William Tucker had two children, William and Hannah. This William was affected by 'swollen legs' and 'attacks'. He died in 1870. Hannah also had 'swollen legs' and 'attacks'. She died in 1864 when 70 years of age. She had married a Mr. Wherrell, and our patient is one of her descendants.

Children of William Tucker, junr.

GENERATION 3.—William Tucker, junior, had two children, Eliza and Alfred. Eliza had 'swollen legs' and 'attacks'. She married, but had no children, and died in 1860 of scarlet fever. Alfred is still alive, and is quite free from the swollen-leg complaint, as are his children also, so far as we have been able to trace them.

Children of Hannah Wherrell (née Tucker).

Hannah Wherrell, daughter of William Tucker, senior, had the following children: Elizabeth, Henry, Mary, Hunsley, William, Harriet, and Lucy.

Elizabeth, who had 'swollen legs', went to America, and is thought to have been drowned.

Henry is alive now, aged 75, a cowman by occupation. He was first troubled by his swollen legs when he was 9 years old. The oedema was persistent, but was kept under control by bandages. At 20 years of age he had his first 'acute attack', similar to those of our patient, and he has had many 'acute attacks' since, though the last one was 25 years ago. He is hale and hearty, notwithstanding his age. The swelling affects the dorsum of the feet, and the legs nearly to the knee, where it stops suddenly. The accompanying photograph (Fig. 3) does not make the swelling very apparent, because the patient keeps his legs constantly bandaged, knowing what a size they get if the bandages are left off. The creases caused by the bandages show fairly well. Some months ago this man had to take some cows to the local market, and in running after them his bandages came off and could not be replaced; on returning home at night the legs, up to the knee, were a great size, but there was no opportunity of getting a photograph of them then. The vigour of the man, notwithstanding his age, is shown by the way he could run after the cows.

His children, George, Thomas, Henry, Silas, Alfred, Bessie, and Ellen, are mentioned again below.

Mary was normal and had two normal children.

Hunsley was herself normal, but of her six children, Ellen, Rose, Emma, and three more, one (Ellen) had the 'swollen legs' and 'acute attacks' (vide *infra*).

William was free from oedema, and died of phthisis, childless.

Harriet suffered from girlhood with the 'swollen legs' and 'acute attacks'. She died in her first confinement, and the child was stillborn.

Lucy is normal, and has a normal child.

Children of Henry Wherrell.

GENERATION 4.—George Wherrell is alive and in good bodily health, but he is of extremely poor intellect. He is free from oedema, but he is so dull and slow that he is barely able to earn his living, and he is the butt of his fellow-workmen. He has two infant children, neither of whom has the hereditary complaint so far.

Thomas Wherrell, who is now 48 years of age, has the 'swollen legs' to a moderate extent and has also had the 'acute attacks'. His present condition does not show any better in the photograph (Fig. 4) than does that of his father Henry, and for the same reason, namely, that the legs are kept constantly bandaged. The trouble is more marked in the right leg than it is in the left, but both legs are affected up to the knees and not higher. The photograph was taken immediately after the removal of bandages; it shows the creases and folds of the latter. His intellect is fairly good, but he lacks enterprise and energy; so much so that he gave up a position of trust and took one in which the wages were less in order to escape responsibility. The swelling of the legs was first bad when he was 18 years old. On three occasions during the last two years he has had 'fits', which we have not seen but which have been described by a person who saw one of them. About 7 p.m. he went out to his allotment and was talking to a man when he suddenly fell down and struggled with both arms and both legs, and frothed at the mouth. The convulsion lasted about 20 minutes. On recovery he had no knowledge of what had happened. It is possible that the attack was epileptic. On the last occasion he was going down a ladder when the seizure came on. He fell to the bottom and contused himself severely. He says that for two days before a 'fit' comes on he has 'a catch in his voice'.

We have notes of two 'acute attacks' in his legs, similar to those we have described in his daughter Alice. On November 10, 1904, at 11 a.m., when at his work, he was suddenly seized with pain in his right groin. This was immediately followed by shivering. He next had pains in the back and hip. On examination there was a large painful swelling at the back of the right thigh, and the right knee was red, painful and a little swollen. There were no varicose veins, though some of the veins looked unduly full. The upper part of the leg was normal. The lower third of the leg, the ankle, and the foot were swollen, red, and painful. Next day the patient's temperature was 100° F., the pulse rate 100, and the respiration rate 28, per minute. There was no abnormality in the cardiac sounds; indeed all the visceral system seemed natural. The thigh was now less swollen, and the knee both less swollen and less red. The foot and ankle were still red and swollen, but no longer painful or tender. On November 12 the temperature

was 100·2° F., the pulse rate 90, and the respiration rate 24, per minute. Herpes had now developed on the lips and nose. The swelling of the thigh had almost gone, the knee seemed normal, and the swelling of the foot and ankle was less, and could be pitted on pressure. The redness had spread higher up the leg. On November 13 his temperature was 99° F., his pulse rate 80, and his respiration rate 20, per minute. There was an area of redness over Scarpa's Triangle on the right side, extending thence down the course of the femoral vessels and round to the popliteal space. On November 14 the temperature had fallen to normal. The redness above the knee had all gone except for a little at the upper part of Scarpa's Triangle. The foot and leg were less swollen and less red. The next day the patient had returned to his normal state of oedema, the 'acute attack' having lasted four days, and having got well spontaneously without leaving additional oedema behind it.

The second 'acute attack' that has been watched began on May 31, 1907. On leaving work at 6 p.m. he began to shiver, and on the way home he vomited. The shivering continued until 8 p.m., when he became very hot. His right leg, which had been aching since 4 p.m., began to swell worse at 8 p.m. Next morning his temperature was 103° F., and his pulse rate 108 per minute. The right leg was hot, more swollen than usual, and painful up to the upper border of the patella. Two days later, June 3, the temperature was 98° F., the pulse rate 78 per minute, the pain in the leg was gone, and the swelling was almost back to its usual amount.

These attacks are all of the same character, and as transient as they are severe for the time being.

Henry was himself normal. His descendants, if any, are not known.

Silas has no swollen legs. He had convulsions in infancy. He is slow in speech and movement, but healthy.

Alfred is normal.

Bessie began to have 'swollen legs' when 9 years old, and the swelling steadily increased till it reached the hips, as in our own patient. She also had several of the 'acute attacks', but we have not been able to get any good account of them. She married, took to drink, and died in 1901, leaving five children, of whom one, a girl, has the 'swollen legs' already. The children are in Egypt and we have not been able to obtain further particulars of them.

Ellen is normal.

The children of Mary Wherrell.

Mary, the daughter of Hannah Wherrell, had two children, both of whom were free from the leg trouble.

The children of Hunsley Wherrell.

Hunsley, the daughter of Hannah Wherrell, had six children.

Of these, Rose, Emily, and three others were all normal.

Ellen suffers both from the 'swollen legs' and from the 'acute attacks';

we have been allowed to examine her by kind permission of her medical attendant, Dr. Mead. She is now 39. Up to 21 years of age she was perfectly healthy, and then, apparently without cause, her legs began to be affected by the family complaint. As far as she can remember, the trouble was first noticed at the level of the knees and thence very gradually spread down to the feet and toes. Her first 'acute attack' was when she was 36, fifteen years after the seemingly causeless oedema began. The 'acute attacks', though so long delayed in their first onset, are now very frequent, the longest interval between them having been three months, except during her last pregnancy, when she had none. Both legs have been attacked; on one occasion the left leg was seized before the right had quite recovered, but otherwise each 'acute attack' has been strictly unilateral. She herself says they come on either just before or just after the monthly period. They begin with a desire to yawn and stretch repeatedly, after which there is a shivering fit and intense pain in the groin. The shivering lasts about 15 minutes, the hands go blue, and the leg goes red, hot, and more swollen than its average. She has to stop in bed for three days, after which she is able to get about again, though not really well for a day or two longer.

Her present condition is as follows: The toes are swollen on their dorsal aspect; there is a deep tranverse sulcus marking the site of the metatarso-phalangeal joints; the plantar surfaces of the feet are almost normal, but the dorsum is swollen and rounded with a deep sulcus over the anterior aspect of the ankle joint; the calves are uniformly swollen, notwithstanding constant bandaging; the patellae and the outlines of the bones at the knees cannot be felt; the thighs are much enlarged, the swelling extending as high as Poupart's ligament on both sides and there suddenly ceasing. The vulva is not involved. There are no ulcers nor sore places. The patient unfortunately refuses to be photographed, and we regret this most particularly because she exhibits the condition much better than do any of the other cases we have photographed, except Alice Wherrell herself. Measurements of Ellen's legs, taken September 17, 1907, immediately after removal of the bandages she always wears, are as follows:—

Maximum circumference measurements.

	Right leg.	Left leg.
Instep	$9\frac{7}{8}$ inches.	$9\frac{7}{8}$ inches.
Calf	$17\frac{1}{2}$ „	17 „
Knee-cap	$16\frac{1}{2}$ „	17 „
Middle of Thigh	$19\frac{1}{2}$ „	$20\frac{3}{4}$ „

The patient's height is 5 feet $0\frac{1}{2}$ inch.

William and Harriett, children of Hannah Wherrell, died childless.

The children of Lucy.

Lucy, daughter of Hannah Wherrell, has one child, who is still young; it has so far escaped from the 'swollen-leg' complaint.

The children of George Wherrell.

GENERATION 5. These are two infants who, as yet at any rate, show no tendency to swollen legs.

The children of Thomas Wherrell.

Thomas Wherrell has five children, two of whom have the complaint.

Alice, aged 18, is the patient whom this paper centres round, and whose condition has been fully described above.

Mary, the next younger, is at present normal.

Edith, the next younger, is at present normal.

Emily is now 12 years old, and has begun to develop the swollen legs. Their condition is not as yet very bad, but they have to be kept constantly bandaged or they would swell out of bounds. The accompanying photograph (Fig. 5) shows very clearly the depressions produced in the oedema by her boot. The swelling is symmetrical, does not affect the feet so much as it does the legs, and stops suddenly just below the knees. The general health and activity are good. No cause could be assigned for the oedema. Emily has, like her father and sister, been subject to what we have called 'acute attacks', one of which was observed. It began on July 6, 1906, at 6 a.m., with a shivering fit which lasted till 8 a.m. She vomited, complained of headache, and had a pain along the outer aspect of the right thigh. At 9 a.m. her temperature was 101° F. At 4 p.m. her temperature was 103·2° F., and her pulse rate 116 per minute. Her visceral systems all seemed natural. Her right foot was red and swollen. An irregular circle of redness, about 9 inches wide in front and 2 inches wide behind, surrounded the right calf, and felt much hotter to the touch than did the surrounding skin. It did not project like erysipelas. The veins on the thigh and leg became unduly visible, but they were not prominent. A single lymphatic gland, not very big, could be palpated in the groin, and little pellet-like nodules could be felt in the skin around the reddened area. Next day, July 7, the temperature was 102° F., and the pulse rate 96 per minute. The redness of the right leg was more general, the foot more swollen, and a red patch was present over the patella. The patient was very sick, being unable to keep even water in her stomach. On July 8 the temperature was 98·4° F.; the swelling and redness were still present, but considerably diminished. On July 9 the leg and foot were still swollen and faintly red, but not painful. The red patch that had been on the calf was surrounded by minute raised spots, bright red in colour, discrete, and rounded. On July 10 the leg began to ache during the afternoon; during the night it 'burned', and on July 11 it was red and swollen as at first. The temperature of the reddened skin was 99·4° F. when taken with an ordinary clinical thermometer under a pad of wool, whereas that of the left leg taken in the same way was 95·4° F.; the mouth temperature at the same time was 102° F. On July 12 the mouth temperature

was 100° F. By July 16 the redness and pain had almost gone; the swelling persisted, and, as is shown in the photograph, it is present about equally in each leg. A similar 'acute attack' occurred on the left side, beginning on July 18, 1907.

James, the youngest, is as yet normal as regards his legs, but he is subject to epileptic fits.

The children of Bessie.

Bessie, the daughter of Thomas Wherrell, had five children. These are all in Egypt and cannot be seen by us personally. We have made inquiries, and we learn that four of the five are normal, but that the fifth already has the 'swollen legs', which began without apparent cause, and seem to be running the same course as have those of the other members of the family who have been affected.

The children of Ellen the daughter of Hunsley Wherrell.

Ellen has two children, both boys, one aged 10 years, the other 12 months; both of these show no tendency to 'swollen legs' at present, but it is too early to say that they are really free from the complaint.

The relationships between the different individuals we have been able to trace is shown in the Genealogical Tree, p. 317.

The diagnosis in the case of our patient, Alice Wherrell, would have been difficult if the family history had not been so definite; but with that it was clear that the condition was very similar to, if not identical with, that described at length by Milroy in America in 1892, as 'An undescribed variety of Hereditary Oedema', and in France in 1898 and later years by Henry Meige as 'Trophœdème chronique héréditaire'. The only account that we have found of any similar family in England is that of H. D. Rolleston in his paper upon 'Persistent hereditary oedema of the lower limbs', in 1902. The literature contains fairly numerous isolated cases, but the fullest accounts of the condition are given by the authors just mentioned.

Milroy's cases are the most numerous—22 affected persons amongst 97 individuals in six generations. Meige's cases numbered 8 affected persons in four generations. Rolleston's cases numbered 3 in two generations. Our own number 13 out of 42 persons traced in five generations. In France the condition is termed Meige's disease. If priority of description is to count for anything, and if the disease is to be named after a person, it should be called Milroy's disease. If no person's name is to be included in the title it may be well styled 'persistent hereditary oedema of the lower limbs', after Rolleston, until its pathology is better known and a shorter scientific name for it can be devised.

The Differential Diagnosis.

It will scarcely be necessary to go into the differential diagnosis in great detail. This has already been done by Meige in a very able manner. Suffice

it to say that cardiac, pulmonary, renal and haemic causes for the oedema can be rapidly excluded, and that myxoedema, though possibly a real difficulty in some cases, can usually be excluded by the normal conditions of the rest of the body, by the presence of the thyroid gland, by the fact that the oedema is real and not merely apparent, and by the fact that the administration of thyroid extract does not ameliorate the condition of the legs.

It soon becomes clear that there is almost certainly a local cause for the oedema, and the three chief local causes that might produce a similar condition would seem to be:—

(1) Venous obstruction or thrombosis.

(2) Lymphatic obstruction.

(3) Errors in the behaviour of the blood vessels or lymphatics, without there being any actual obstruction to them—vasomotor neurosis.

The relation between the 'swollen legs' and the 'acute attacks'.

Before we can go further with the discussion of the last paragraph it will be necessary to say a word or two as to the relation between the 'swollen legs' and the 'acute attacks' which so many of the above patients have had. If an 'acute attack' were always the first thing, then it would be very difficult to exclude venous thrombosis or lymphatic obstruction, secondary to inflammation, as a cause for the oedema. The remarkable thing is that the 'swollen legs' have come on gradually, without any assignable cause; and in one case the 'swollen legs' had been present for five-and-twenty years before any 'acute attack' occurred at all.

It seems clear, therefore, that the 'acute attacks' are either accidents, or at most concomitants, rather than essential factors in the oedema. We do not know what is the nature of the 'acute attack', and we shall discuss it again when we mention angioneurotic oedema; but we are bound to admit that, though possibly a 'vasomotor phenomenon', each acute attack bears some resemblance to a temporary microbial infection comparable with erysipelas. The rigor, the pyrexia, the painfulness of the part affected, the vomiting that may occur at the same time, all suggest microbial infection. On the other hand, the attacks are remarkably transient, lasting but three or four days; they pass away spontaneously without any particular treatment; and they seem to be quite free from danger, for not one of the patients has died of septicaemia, even when the 'acute attacks' have been constantly repeated. Upon the whole we are inclined to think that the 'acute attacks' are not due to sepsis, or at least that they are not primarily due to micro-organisms, but rather to vasomotor troubles. Be this as it may, our point is that the oedema precedes any 'acute attack', and may precede it by as much as twenty-five years. There seems, therefore, to be none of the ordinary causes of venous thrombosis or of lymphatic obstruction underlying the oedema.

Other reasons for excluding venous thrombosis or lymphatic obstruction.

Besides the above, there are other reasons for excluding venous thrombosis or lymphatic obstruction as the original cause for the oedema. First, there is the distribution of the swelling. The cases recorded by Meige agree with ours in the fact that the oedema receives a sudden limitation at the level of a joint. In Alice Wherrell it for some time ceased at the ankle; we have several cases in which the oedema stops at the knee, and several others in which it stops at the hip or groin. The oedema does not stop gradually, moreover, but suddenly, and does not involve the vulva or the abdominal wall, although it may become extreme immediately one passes down over Poupart's ligament. This would be difficult of explanation if the obstruction were in the pelvis; and, when the swelling is bilateral, it is difficult to understand how any obstructive lesion in veins or lymphatics should be well marked right up to Poupart's ligament on both sides and yet not extend into the pelvis in any single one of the patients recorded by Milroy, Meige, Rolleston, ourselves, or any of the observers we can find. Venous obstruction seems unlikely on this further ground, namely, that the circulation in the affected legs seems to be quite good; a patient over 70 who has had the oedema all his life has been able to run about after cows, so that his muscles must have been well supplied with blood. Visible distension of the veins in the legs is a rarity in the cases. The feet are not unduly cold. It is conceivable that there might be some congenital abnormality in the structure of the lymphatics from Poupart's ligament downwards; but against this view are the facts that it may be twenty years before the oedema sets in, that when it does set in it may be restricted to the level of the knee for years before it reaches to Poupart's ligament, and that when it spreads at all it spreads at one time the full distance from one joint level to the level of the next joint above (Meige). Upon the whole, therefore, although it cannot be called a very satisfactory explanation, we think, with Milroy, Meige, and others, that the oedema in these cases is secondary, not to gross structural changes in the blood vessels or lymphatics, but to an error in the functions of these vessels, presumably, or at least possibly, resulting from erroneous functions in the nerves supplying them —in other words we think the condition is primarily a *vasomotor neurosis.*

The relation of these cases to those of angioneurotic oedema and of other vasomotor neuroses.

There are three well-known conditions in which vasomotor neurosis is generally held to be at the root of the affection. These are Raynaud's disease, factitious urticaria, and angioneurotic oedema.

These are so distinct in their objective manifestations that it would not be at all surprising if other, and at first sight wholly different, manifestations of vasomotor neurosis were possible. Our cases show little in common with Raynaud's disease; that is to say they could scarcely be mistaken for cases

of Raynaud's disease, although, in addition to their oedema, cold weather causes several of the patients to suffer from blueness of the hands, which to some extent resembles Raynaud's disease. Similarly, they could not be taken for cases of factitious urticaria. Nor could they, we think, be taken for a variety of angioneurotic oedema in the ordinary sense of the latter term. Nevertheless, there are distinct points at which angioneurotic oedema and our cases of Milroy's disease come close together—notably in the strongly marked hereditary disposition, and possibly in the 'acute attacks' to which many of the above patients were subject. It seems likely that Raynaud's disease, factitious urticaria, angioneurotic oedema, and Milroy's disease are related to one another pathologically, but that their objective manifestations are so well defined and so different that these different kinds of vasomotor neuroses merit distinctive names. It may be noted that, apart from the 'acute attacks', our cases had absolutely painless swelling of the legs, and no general disturbances of health at all, whereas during the 'acute attacks' there was considerable constitutional disorder, sometimes with marked vomiting for a short time, comparable to the colic, nausea, and vomiting often seen during exacerbations of angioneurotic oedema. So like the latter were the 'acute attacks', except in so far as they were confined to the legs instead of varying in place and affecting body, face, hands, arms or throat, that we felt very much inclined to call them definitely 'angioneurotic attacks'. This, however, we have refrained from doing, because we cannot bring forward absolute proof that they were angioneurotic.

The incidence of other nervous complaints in the family.

It is often a very difficult thing to elicit a history of insanity or fits in a family. Nevertheless it is interesting to observe that Alice Wherrell's uncle George is of weak intellect and the village butt; that her father Thomas has had three 'fits', which seem to have been very like epilepsy; that Silas is slow-witted; that Bessie was a dipsomaniac; that Alice herself has had an attack of garrulous mania, with delusions; and that her brother, James, a young boy, has already had many epileptic fits. A similar history of epilepsy in members of a family in which other members are subject to the trophoedema of the legs has been noted by other observers, and the point is of interest in connexion with the angioneurosis that is supposed to be at the root of the trophoedema.

The points in which our cases resemble, and the points in which they differ from, those recorded by others.

The points in which our cases and those recorded by others closely resemble one another are as follows:—

(1) The restriction of the oedema entirely to the legs.
(2) The absence of any traceable cause for the oedema, general or local.
(3) The strong family predisposition to the complaint.

(4) The painlessness of the pale swollen legs (apart from the 'acute attacks' in our cases).
(5) The absence of constitutional symptoms.
(6) The sharpness of limitation of the upper level of the oedema.
(7) The incidence in both males and females.
(8) The permanence of the oedema when once it has appeared.

There are certain points, however, in which our cases differ from those of others. Meige, for instance, lays stress upon the absence of 'acute attacks', which occurred on more than one occasion in most of ours. Milroy lays stress upon the oedema being present at birth; Meige lays stress upon its appearing at puberty; in our cases not once was it actually noted at birth, and the age at which it first attracted attention was sometimes in infancy, sometimes in boyhood or girlhood before puberty, sometimes not until the teens were passed.

The fact that there are differences such as these is not to be wondered at, seeing that the cases recorded by each individual observer all belong to one family, and are, therefore, likely to resemble one another, but to differ in details from cases arising in a different family observed by some one else. Small points of difference by no means indicate differences in kind; they may well be but family variations in the same condition.

Comparison with muscular dystrophies.

Several observers have aptly compared this disease to that of the muscular dystrophies; the latter may be present at birth (congenital), or they may develop later (hereditary). Similarly, it seems that trophoedema of the legs may be congenital and present at birth, as in Milroy's cases, or it may be hereditary and only develop later at a constant period after birth (puberty), as in Meige's cases, or at a variable period after birth, as in ours.

The treatment of the condition.

Little treatment is required in the majority of the cases, beyond firm and constant bandaging of the legs. Several of our cases lived to over 70 years of age, having suffered from the complaint for 60 years or more, but having kept the swelling in check by constant bandaging.

The 'acute attacks', dangerous though they look, pass away spontaneously in a few days, and all that can be done for them is to relieve the pain by putting the patient to bed and applying anodynes to the affected part.

Our own patient's condition had passed all bounds so far as keeping the oedema in check by bandaging was concerned, and all treatment for the condition was a failure as regards ameliorating it. The oedema always diminished to some extent with rest in bed, and firm bandaging was a relief to the patient when she was able to get up after such rest. Medicinal treatment of various kinds was tried in vain—thyroid extract, diuretics, purgatives, potassium iodide, mercury, intestinal antiseptics, bromides, valerianate of zinc, and so forth. None made

the least impression on the leg condition. One observer has recorded benefit in one case from electrical treatment, and one or two have recommended massage. The latter may alleviate the oedema temporarily, but when the swelling has got beyond bounds, as in the case of Alice Wherrell, it seems next to impossible to restore the normal conditions again. The important point seems to be to recognize the nature of the trouble early, and to keep the legs bandaged constantly from the first, so that no large increase in the oedema can occur. It may then be held in check for a great many years, as may well be seen in the photograph of the two men. These two know full well what would happen if the bandages were long off whilst they were upright, and they will not leave the bandages off at all; otherwise the photographs of them would show a great deal more oedema than they do.

The effects of pregnancy on the condition.

Several female members of the family married when the trophoedema was well advanced. It might have been thought that the oedema of the legs would certainly have been made materially worse by pregnancy. This has not been the case, and in one instance, in which the 'acute attacks' had been frequent previously, they were in complete abeyance throughout a pregnancy. The fact that the leg condition is not made materially worse by pregnancy may, perhaps, be an additional argument against lymphatic or venous obstruction being its cause, and, therefore, indirectly in favour of the angioneurotic view.

Transmission by an unaffected mother.

It is a point that will, perhaps, interest those who pay attention to the family transmission of peculiarities that Hunsley, the daughter of a woman who had the family complaint, was not herself affected, but transmitted the trouble to her daughter Ellen. If one had the opportunity it would be interesting to see whether any of Ellen's children, escaping the trouble themselves, will one day have children who are affected.

Conclusion.

The family of which we have given an account seems comparable, with minor differences, to those described by Milroy, Meige, Rolleston, and others. The chief points in the malady from which certain members of the family suffered—13 out of 42 individuals in five generations—are summarized on pages 326 and 327, the most obvious being painless persistent oedema of one or both legs, arising apparently without cause, and apart from any constitutional ill health. The malady has received various names, of which we select Persistent Hereditary Oedema of the Legs, or Milroy's disease. The disease affects both males and females, and is not itself inimical to life; though in some cases the oedema becomes so like elephantiasis that locomotion is greatly impeded, or even rendered almost impossible, as in the case of Alice Wherrell. There is often a history of epilepsy or other nervous disorder in the same family. Our cases, unlike those

of some observers, were subject to what we have described as 'acute attacks', many of which we have described in detail. The condition differs objectively very much from Raynaud's disease, factitious urticaria, and angioneurotic oedema, but we think that there is evidence that underlying both these three conditions and our cases of Milroy's disease there is a common pathology, namely that of a vasomotor neurosis.

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DESCRIPTION OF PLATES

FIG. 1. Alice Wherrell, Persistent Hereditary Oedema of the legs.

FIG. 2. Alice Wherrell, Persistent Hereditary Oedema of the legs.

FIG. 3. Henry Wherrell, grandfather of Alice. The leg-bandages have just been removed. The Oedema has been present for 66 years.

FIG. 4. Thomas Wherrell, father of Alice. The leg-bandages have just been removed. The Oedema has been present for 30 years.

FIG. 5. Emily Wherrell, sister of Alice. Persistent Hereditary Oedema of the legs is beginning to develop.

FIG. 1

FIG. 2

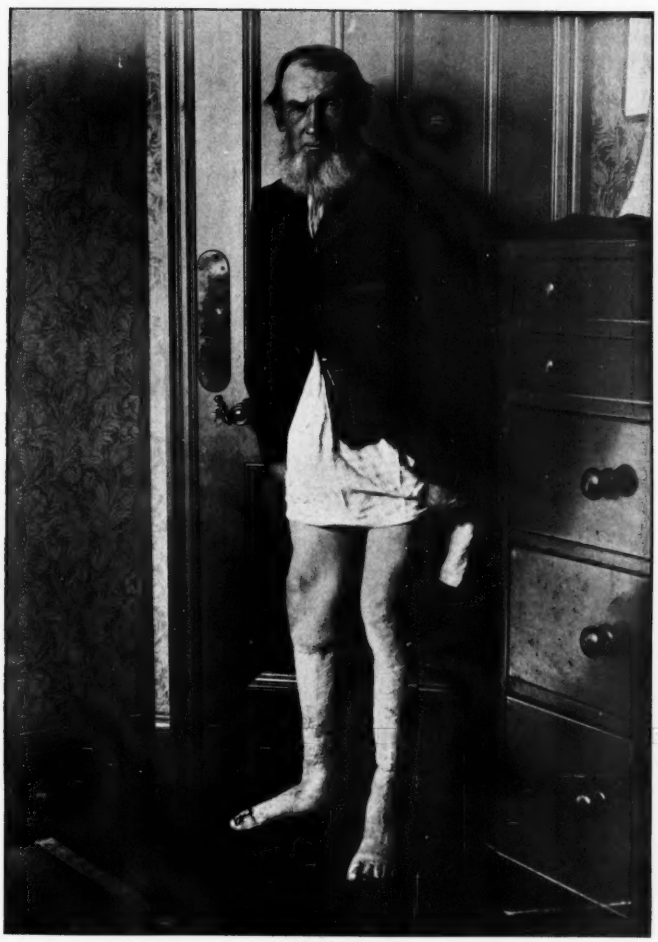


FIG. 3

FIG. 5

FIG. 4

THE INHERITANCE OF CERTAIN HUMAN ABNORMALITIES

By A. M. GOSSAGE, M.D., Oxon., F.R.C.P.

Physician to Out-patients at the Westminster Hospital and the East London Hospital for Children.

The study of Heredity has an absorbing interest for everybody, but to no one should it appeal more than to the physician. From the earliest times he has been prone to regard constitutional inheritance as an important factor in the incidence of disease amongst his patients, and also in the treatment of disease. His facts, however, have in the past been somewhat loosely collected, and naturally the conclusions drawn therefrom have been either vague or unjustified. More scientific methods of investigation have recently arisen in biological research, and have led to important and well-founded deductions in plants, animals, and men. Of these methods, two at present are chiefly employed by biologists. In the first—the statistical method of the biometricians—data of the inheritance of a particular quality are collected from a large number of individuals, collated, and then conclusions drawn. This method has supplied some very valuable results both in animals and man, and by it Professor Karl Pearson and his followers have heen able to prove that both physical and mental characteristics are directly inherited from parent to child in a certain definite proportion. For instance, the children of tall parents have more chance of being tall than the children of ordinary people, and this chance can be represented by a definite number. In the same way, clever parents tend to have clever children, and the offspring of the consumptive show a definite tendency to be attacked by phthisis.

The other method of investigation is an experimental one, where individuals exhibiting a certain quality are crossed with others, some possessing the quality and some not, and the proportional representation of the quality is noted amongst the offspring. This method owes its importance to the rediscovery in 1899 of the law which Mendel had been led to enunciate more than thirty years before as a result of his researches on peas. Mendel's law may be roughly stated as follows: certain qualities of living organisms may be arranged in opposing pairs (allelomorphs); both members of an allelomorphic pair may be present in a single organism, being each derived from a separate parent, with the result that the organism as a whole may exhibit only one of these qualities

[Q. J. M., April, 1908.]

(which is then said to be dominant) or some combination of the pair; both allelomorphs are present in every cell of the organism except in the germ cells or gametes, where the allelomorphs separate from one another, so that each gamete possesses only one member of the pair, and of the total number of gametes half possess one allelomorph and half the other: separate pairs of allelomorphs segregate independently of one another as a rule. In breeding, the fertilized ovum is formed by the union of a male and a female gamete, each of which carries its one allelomorph, and the quality in the offspring depends on the nature of these allelomorphs: e. g. the descendant may have two similar allelomorphs, in which case it would be pure with regard to the particular quality; or two dissimilar ones, as in the instance already given, when it would probably exhibit the quality of the dominant allelomorph, but be impure. This law has been shown to hold good in a very large number of instances in the animal and vegetable kingdoms, and with its aid some very complicated facts of inheritance have been elucidated.

The application of this experimental method to human beings presents many difficulties. To begin with, breeding experiments cannot be arranged, and the investigator is dependent on the haphazard experiments of human marriage. Then the purity or impurity of an individual with regard to a certain quality cannot be ascertained in the absence of progeny, for it is by his children that a man is known. Human families are small, and there is an immense waste of generative cells which are never fertilized. Children are born one at a time, and after the birth of each child the probabilities for a particular combination of germ cells for the next child are not changed by the previous birth. In such small families, therefore, we cannot expect the numbers of the children exhibiting the separate qualities to conform with the theoretical forecast, but when a number of families are grouped together the results ought to approximate to expectancy. The easiest condition to investigate is that of some marked quality, the presence or absence of which is obvious. An example of such a condition is afforded by brown-eyed people who possess pigment in front of the iris, which pigment is absent in the blue-eyed. The brown eye has been shown to be dominant to the blue eye by Hurst, so that brown-eyed children have always one parent with brown eyes, two brown-eyed parents may have a blue-eyed child, but two blue-eyed parents should breed true. Most of the conditions that are easy to investigate are uncommon, consisting of congenital abnormalities, and one observer has thus little chance of meeting more than a few families, and so has to depend for his data on the published observations of others. Unfortunately, in the recording of cases, the heredity factor has been only one of the points on which stress has been laid, and the recorder has often been content with mentioning the number of similar cases in the family, without giving the number of normal individuals. Further, the patients, from whom the facts have to be collected, belong usually to the less intelligent classes, whose memory as to their own children is frequently defective, while it is still more so with regard to the families of their parents and

grandparents. An abnormal child is more likely to be remembered than a normal one, so that an excessive number of abnormal individuals must be expected. In spite of the difficulties, however, the law has been found to hold in a fair number of instances, such as the inheritance of certain congenital abnormalities of the eye, which Nettleship has collected with such care. It becomes, therefore, a matter of interest and importance to investigate the family histories of other abnormalities, and to see how far they correspond with the law.

Certain defects of the skin show a remarkable tendency to be handed down from parent to child, and so promise a fruitful field for investigation. I have myself recently come across a family afflicted with a peculiar horny condition of the palms and soles. This abnormality is a marked one, is apparently always directly handed down from parent to child, and a fair number of affected families have been described, while the family records have been exceptionally well given; here, therefore, is a simple problem for elucidation. The condition is described under a number of names as Ichthyosis, Keratosis, Keratoma, or Tylosis of the palms and soles. It consists in an abnormal thickening of the epidermis on the palms of the hands and palmar surface of the fingers, on the soles of the feet and plantar surface of the toes, and the thickening is limited to those parts, not spreading to the dorsal aspects of the hands and feet, and not being found elsewhere over the body. In the vast majority of cases the condition is noticed soon after birth, though occasionally it has not been observed until the age of 5 or 6 (Böhm), but this is so rare that one is almost justified in concluding that the condition was present, but unnoticed, during infancy. In a large number of cases no inconvenience is caused to the affected people, but sometimes painful fissures appear, which may become infected, causing cellulitis and lymphangitis (Decroo), while in other cases the epidermis is shed in the autumn, leaving a tender surface which quickly becomes re-covered by excessively thick epidermis (Crocker). Some recorders have noticed an excessive secretion of sweat in their cases (Thost, and Unna), while others found a diminution of sweat (Decroo, loc. cit.). There seems to be no marked alteration of sensation beyond a slight dulling due to the thickness of the epidermis (Decroo), though Thost says that in his family the feet were so tender that none of the members could walk barefoot. A similar horny condition of the palms and soles may be acquired in adult life from hard work, local irritants, arsenic poisoning, and in association with hyperidrosis, but this acquired condition is never handed on to the descendants.

Of the family already mentioned, I myself saw two members with this condition. A woman, aged about 45, brought her son, aged 8, to the East London Hospital for Children, as he was suffering from scarlet fever. The palms and soles of both mother and son were found to present a remarkable horny condition of the skin which caused them no inconvenience, and was not associated with excessive sweating or any other peculiarity. In both cases the abnormality had existed from birth. The mother's father and paternal

grandmother had been similarly affected, while her father's sister had been quite normal. Of the woman's own family of 7 children, 2 males and 2 females had a similar condition of the palms and soles, while 3 females were unaffected. In medical literature I have been able to find 45 families afflicted in this way, but closer investigation shows that a number of these families should be eliminated. First come the 5 families described by Neumann from the island of Meleda in the Adriatic. In consequence of these cases, the condition here described has often been called the mal de Meleda, but, as Vorner has pointed out, Neumann's cases differ clinically from tylosis palmaris et plantaris in that the horny condition affected the backs of the hands and feet, and other parts of the body. As the mode of inheritance is also different, for the affected individuals were generally born of unaffected parents, we are justified in excluding his cases. A complete study of the mal de Meleda from the hereditary point of view would be of great interest and value; at present the reported cases are too few and too incomplete for any conclusion to be formed. The family described by Sämberger should also be

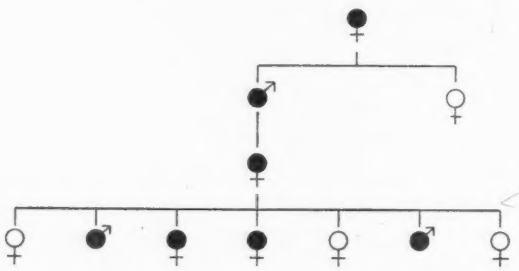
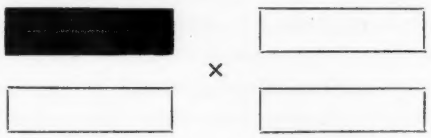


FIG. 1. *Tylosis palmaris et plantaris.* Author's family.

omitted, as the abnormality did not appear until the age of 8, and only the feet and not the hands were affected. The condition in this family was directly handed on from parent to child, but a very small proportion were sufferers. The patient's father and grandfather suffered, but his 12 brothers and sisters were quite free.

This reduces the number of families to 39, and of these 10 are so incompletely reported, or consist of so few members, that they are of small value for our purposes. Another family, that reported by Ballantyne, has also to be put on one side, for reasons that will be mentioned presently. Examining the records of all the 39 families, it is found that the condition is handed down directly from parent to child, that it equally affects males and females (166 males to 140 females), and that it is transmitted equally through males and females (66 males transmitted the condition to some of their offspring, and 52 females). These characteristics suggest that the abnormal condition is dominant to the normal. Owing to the fact that the

affected people are constantly crossed with normal, none of them would be pure dominants, that is to say, they all contain one of the dominant allelomorphs and one of the normal recessive allelomorphs; while the normal individuals are pure recessives containing two recessive allelomorphs. This can be diagrammatically represented as below, where the black represents the dominant allelomorph:



On sexual intercourse taking place with a normal individual, half the gametes of such an abnormal person will contain the dominant allelomorph and half the recessive, whereas all the gametes of the mate will be recessive. It is an even chance, therefore, whether an individual gamete of the normal mate will be impregnated by a normal or an abnormal gamete, and if a number of children

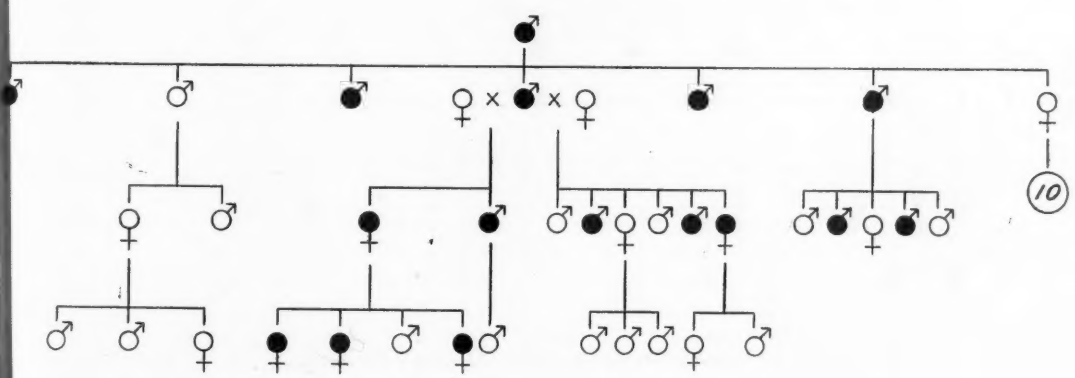


FIG. 2. *Tylosis palmaris et plantaris.* Thost's family.

result from such intercourse the proportion of normal and abnormal amongst them should be approximately equal, and the numbers should be still nearer equality if several families are reckoned together. In the 28 families which are sufficiently fully reported for use, omitting the earlier generations as being obviously incomplete, we find that 222 children of individuals afflicted with tylosis of the palms and soles were abnormal, and 184 normal. This is sufficiently close to the theoretical equality, allowing for the expected excess of abnormal for the reasons already given. Further, the abnormal offspring should transmit their abnormality to half their progeny, whilst the normal should never transmit the abnormality. This is borne out in these families with one ex-

ception. We are justified, therefore, in regarding tylosis of the palms and soles as a dominant Mendelian allelomorph to the normal condition.

It has been pointed out that these abnormal individuals are none of them pure dominants. Pure dominants would be expected to arise from the conjunction of two such abnormal persons, in the proportion of 1 pure dominant, 2 impure dominants, and 1 recessive, but there is no record of any intermarriage of this kind. The only other way in which we can imagine pure dominants to arise is by a marked mutation *de novo*. A pure dominant should transmit to all his children, since every recessive gamete would be impregnated by a dominant gamete, and all the offspring would be impure dominants. It is interesting to note that in the two cases where the condition definitely started *de novo*, both parents being normal (Jacobi), all the descendants of the abnormal persons were similarly affected. The numbers of such further offspring are too small however, to warrant any conclusions being drawn, being 2 in

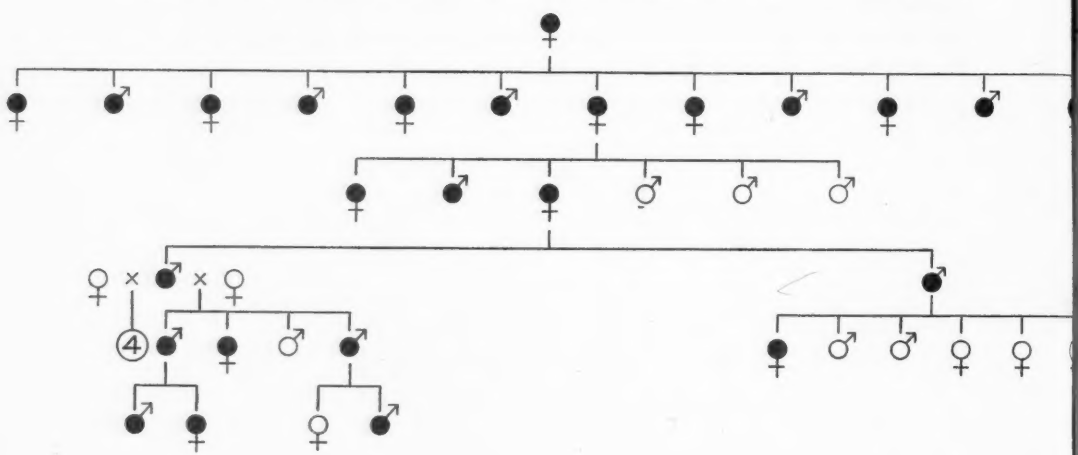


FIG. 3. *Tylosis palmaris et plantaris.* Jacob and Fulton's family.

Jacobi's case and only 1 in Schotz's case. In the family reported by Jacob and Fulton, the affection is somewhat definitely stated to have first appeared in a woman whose mother accounted for her baby's condition by having gazed intently at some fish while pregnant. It is possible, therefore, that this was a case arising *de novo*, and it is noticeable that all her 12 children were affected. (See Fig. 3.)

There is one family (Ballantyne) which is not in agreement with the view put forward here, since the condition, which had existed in the family for generations, was said to affect only the females and to usually skip a generation. The patient's mother was said to be normal, but the patient transmitted the abnormality to her daughter, while her son was unaffected. This patient may have been mistaken, or possibly some other factor is necessary

for the condition to show itself, such factor being only very rarely absent from normal people. In two other instances it seemed possible that a generation was skipped in the inheritance. In Horton Dale's family, the brother of the original patient had an affected child, while nothing is said about the brother himself; Vorner concludes that he was not affected, but Ballantyne, writing much nearer the time of Dale's paper, definitely says that he was affected; so that we may conclude that a generation was not skipped. The report of Ehrmann's case leaves a doubt as to whether the mother of the patient was or was not affected, but Prof. Ehrmann has kindly informed me that there is a misprint in this report, which should read: 'In der Familie ist dieselbe Erscheinung beim Urgrossvater, der Grossmutter, der Mutter, bei 6 Brüdern der Mutter und 3 Schwestern der Patientin vorhanden; 4 Schwestern *der* Mutter und 1 Bruder der Patientin sind davon verschont.' Ballantyne's family,

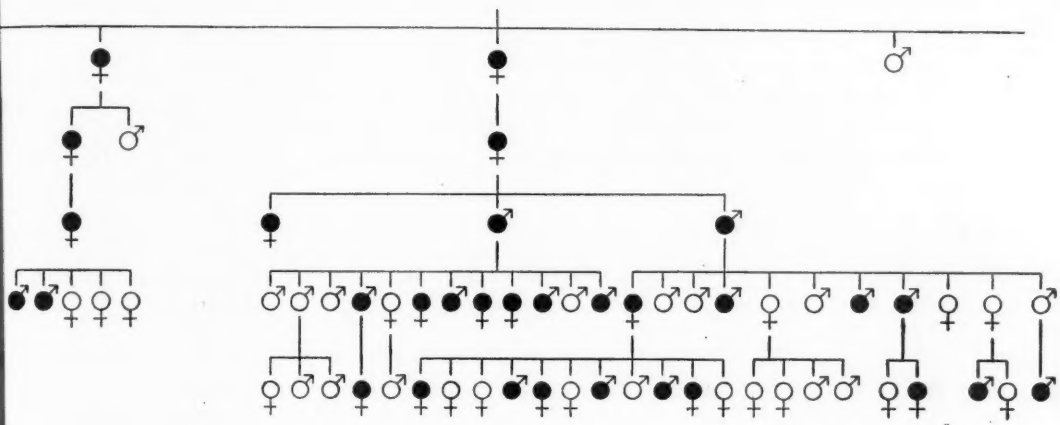


FIG. 4. *Epidermolysis bullosa.* Bonajuti's family.

therefore, is the only one where a generation is skipped, and as the affected and unaffected are approximately equal in the families of the affected we may be certain that the opposing allelomorphs are equally divided among the gametes.

Inheritance is the most important factor in a number of other peculiarities of the skin, but in many of these the families are too few and too small for any definite conclusions to be formed. As a rule, the abnormal condition seems to be dominant to the normal (Waelsch, Colcott Fox, and Wilson). The condition of multiple hereditary telangiectasis seems also to be a dominant to the normal condition. Unfortunately, the family histories in this interesting complaint are not very full, the normal individuals being evidently left out in many of them. In three instances there are fairly full records (Wickham Legg, Parkes Weber, and Kelly), and in these the numbers are: affected 14,

and unaffected 27. It has to be remembered that the complaint does not show itself in early life, and that many of the children therefore die young, before an opportunity has been afforded for ascertaining whether they were really free from the family complaint. This, no doubt, gives a partial reason for the great excess of the unaffected. There is, too, a probability that in Parkes Weber's family the condition had been handed down through an unaffected individual.

Dr. Walter Bell, of Lowestoft, has kindly sent me a record of a family in which tightly curled, short, woolly hair of the negro type tended to occur, although the features were not in the least negroid. A tradition in the family attributes the peculiar hair to a 'Mexican' ancestor several generations back. The peculiarity was transmitted directly, was found in both males and females, and half the children of the affected had the abnormal hair (18 affected

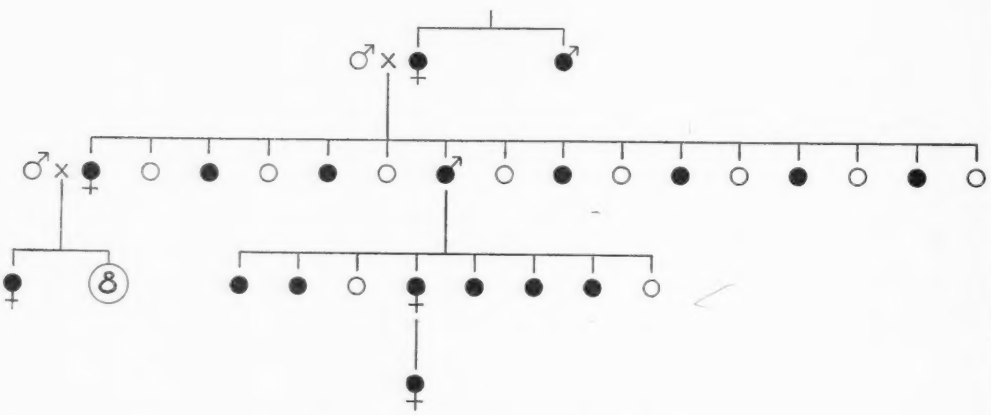


FIG. 5. *Curly hair.* Dr. Walter Bell's family.

to 18 free). See Fig. 5. Rizzoli (quoted by Stricker) gives a remarkable family history of the inheritance of a tuft of congenitally white hair over the brow through six generations. This was handed down directly from parent to child, and of the progeny of the affected 15 were also affected, and 15 free. See Fig. 10. Morgan and Godlee give records of a similar inheritance of a tuft of white hair in each family through four generations, where the inheritance was direct from parent to child. Unfortunately, neither of them say anything about the unaffected members of their families. This abnormality of the hair, as well as that described by Dr. Bell, seems to be a simple dominant.

Some very remarkable family histories have been published concerning the condition to which Köbner gave the name of Epidermolysis Bullosa. This is essentially a congenital abnormality of the skin which shows itself soon after birth in a peculiar response to slight irritation, by the formation of bullae

filled with clear serum. Hallopeau distinguishes two forms: one with merely the eruption of bullae and no subsequent trophic changes (though Herzfeld noticed alterations of the nails), and the other with marked trophic changes in the nails, and scarring and atrophy of the skin after the bullae; miliary cysts, containing broken-down epithelium, tending to develop after the disappearance of the bullae in the latter form. The two forms are evidently closely connected and give similar family histories, and so may be considered together. The seats of selection for the bullae are the hands, soles, knees, and elbows, but they may form anywhere, even in the mucous membrane of the mouth. The records of these cases show certain striking differences from those of tylosis of the palms and soles. There are, for instance, a very much larger number of cases in which heredity apparently plays no part, and a much larger number of cases whose parents were quite healthy. The skipping of a generation, too, is a comparatively frequent occurrence in the family histories (cp. Bonajuti, Colombini, and Török). In the majority of cases, however, the condition is directly inherited, affects males and females alike, is transmitted equally through males and females, and attacks about half the progeny of those capable of transmitting it (180 affected to 209 unaffected, in 27 families). It is noticeable that the expected excess of affected is not found, the reason evidently being that some of the unaffected are capable of transmitting the condition to their offspring and so should be included amongst the affected. We are, however, justified in concluding that the opposing allelomorphs are divided equally amongst the gametes.

Examples of heredity of a similar character to that in epidermolysis bullosa have been met with in both animals and plants, and the reason of the capability of some of the unaffected to transmit has been worked out experimentally in several instances. It is, for instance, possible that the dominant allelomorph may occasionally not show itself, though present, as appears to occur with extra toes in fowls (Bateson), or it may be necessary for the exhibition of a particular characteristic that two factors should be present together; or again, an inhibiting factor may be present in individuals who would be expected to exhibit the characteristic but do not do so. It would be attractive to speculate on the explanation of the heredity in epidermolysis bullosa and other similar conditions in human beings, but, in the absence of the proper conditions of experimental research, the explanation would be pure speculation and incapable of proof.

The family records of xanthoma give somewhat similar results to epidermolysis bullosa. This condition is characterized by the appearance of yellow patches on the eyelids, and sometimes by the eruption of yellowish papules all over the body. The two forms may be conjoined, or may occur separately. They most commonly occur sporadically in association with jaundice, but both forms may be inherited. When inherited, the first appearance may take place in early childhood, or may be delayed until puberty, these peculiarities being characteristic of the particular families in which they occur, i. e. early appear-

ance in one family, late in another. There are 7 families sufficiently fully given for conclusions to be drawn, and the numbers come out 34 affected to 35 unaffected. The condition is sometimes transmitted through the unaffected (cp. Török and Church).

A tendency to early baldness, with the development of moniliform hairs, monilithrix, also tends to occur in families. The number of families recorded are few, only 5, and 2 of these (Hallopeau and Lefevre; Beatty and Scott) are evidently incomplete. In the other 3 families the number of affected is 31, and of the unaffected 30. There seems a definite skipping of a generation in Beatty and Scott's family, so that this condition is very similar to epidermolysis bullosa.

Hypotrichosis congenita familiaris is an affection where children are born without hair, or in which the hair disappears in the first few months of life, never to reappear. This affection is recorded as appearing in 7 families, and, as in the other conditions described, appears to be dominant to the normal. In these families there were 26 affected and only 10 free, but it is evident that in several of the families the normal individuals have not been mentioned. Since several affected children in one family have been born to healthy parents, it is probable that the inheritance of this affection is similar to that of epidermolysis bullosa.

Similar family histories are afforded by the cases of enlarged spleen, quoted by Cowan in the *Quarterly Journal of Medicine*. Here the affected are 21 and the unaffected 42, the great excess of the latter being probably partly explicable by the large number of children who died in infancy before they had an opportunity of developing the family complaint. In these families a generation seems to be sometimes missed, and on several occasions more than one affected child has resulted from the union of healthy parents.

The condition of polyuria and polydipsia, to which the name of diabetes insipidus has been given, is again of a similar character when it is hereditary. Gabriel Pain's family is too incomplete for use, there being no mention of the normal members, and the families reported by Lacombe and Orsi are probably also incomplete, but have been included. In the 4 families which I have grouped together there were 43 affected to 50 unaffected. In Gee's family there are 3 instances of a generation being missed, the abnormality appearing again in the grandchildren.

In 1893 a peculiar and hitherto unknown skin affection was independently described by Mibelli and Respighi as occurring in the province of Parma in Italy, and they occasionally described the same cases. In this condition a raised horny ridge appeared on the skin, which spread centrifugally while the centre became depressed, and was characterized by atrophy of the constituents of the skin. Mibelli called the condition Porokeratosis, believing that it started from the sweat glands, while Respighi denied this, and proposed the name Hyperkeratose figurée centrifuge atrophiante. Several further cases were recorded, and in most of them it was found that the condition was a family peculiarity. The transmission was always direct from parent to child, and, so far, no case of a generation

being skipped has been recorded. On several occasions, however, more than one member of a family has been affected while both parents were quite healthy. It is noticeable that the number of unaffected is much higher than in the other conditions which have been considered, there being 72 unaffected to 48 affected in 10 families. It must, however, be remembered that the affection first appears in adult life, and that several who might have been affected had died young, before the condition had had time to develop. This explanation, however, will not hold in the case of a family, the record of which has been kindly sent me by Dr. Walter Bell. In this family, heterochromia of the iris tended to appear when one eye, always the left, was 'greyish blue in colour, with chestnut-

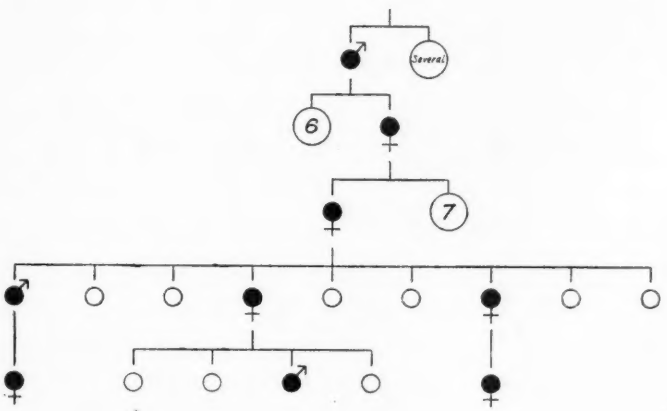


FIG. 6. *Hetero-chromia of iris.* Dr. Walter Bell's family.

brown patches'. Of the offspring of the affected members of the family, 8 were affected and 22 free. (See Fig. 6.)

General ichthyosis and ichthyosis follicularis both tend to occur in families, but it is difficult to bring the records into line with one another. For instance, Byron Bramwell, in one family with ichthyosis, finds the condition directly transmitted to 3 out of 5 of the children of an affected person, while in another family there was a tendency to the sporadic occurrence of ichthyosis without the parents of the sufferers being affected. Again, ichthyosis is said to often occur in several members of a family without there being any hereditary influence (cp. for instance, Gaston). Lameris and Bond both describe families in which it occurred only in the males, but was handed down through unaffected females. I have myself recently come across a family several members of which suffered from general ichthyosis. In the diagram of this family, given in Fig. 8, it will be seen that the condition has been handed down from an affected grandfather to 2 out of 6 grandchildren, through an unaffected son.

In the various families that have been considered in this article, there tends

to be an equality between normal and abnormal in the offspring of abnormal individuals, and the abnormality tends to be handed down directly from parent to child (though to this there are a number of exceptions), and we are, therefore, justified in concluding that the inheritance is conducted on Mendelian lines, the

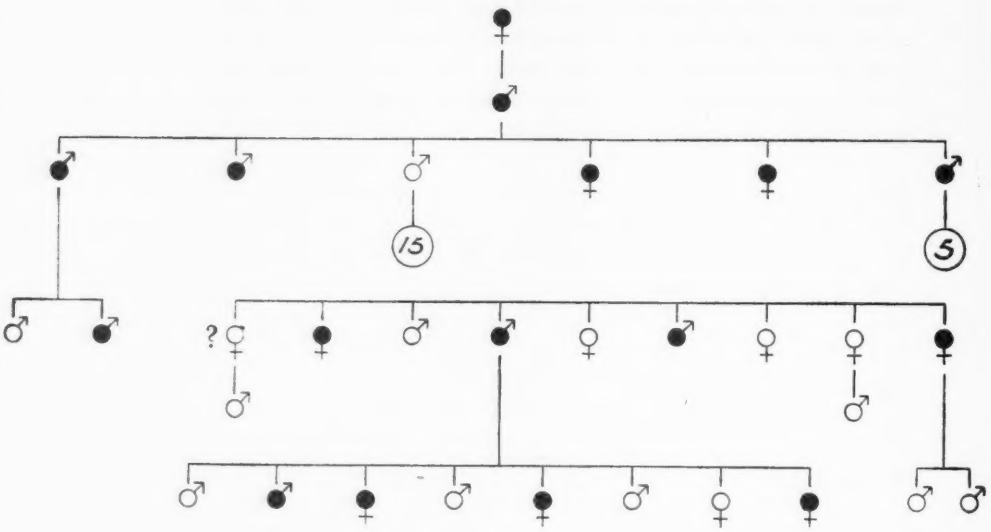


FIG. 7. *Monilithrix.* Sabouraud's family.

abnormality being a dominant allelomorph to the normal. In cases such as porokeratosis or multiple teleangiectasis, where there is a large excess of the apparently normal in the offspring, it is not improbable that this excess is to some extent only apparent, owing to a number of individuals dying before the period

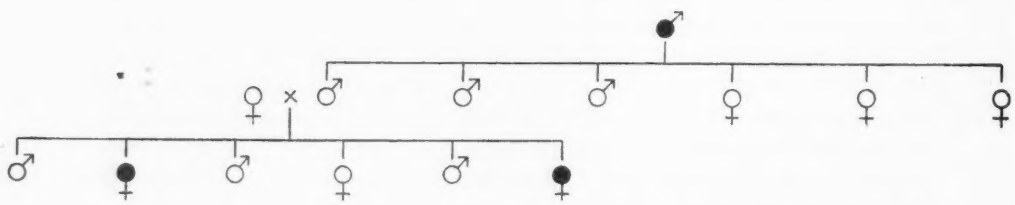


FIG. 8. *General Ichthyosis.* Author's family.

of life when the abnormality shows itself, a proportion of such prematurely dead persons really having the family abnormality. The number of families here considered is, unfortunately, very small, and for the satisfactory proving that heredity may be of this Mendelian type a very much larger number is required.

The facts are however suggestive, and we may hope that future records may firmly establish this explanation, especially if these records are more complete than those at present available. Our profession should now recognize that in the

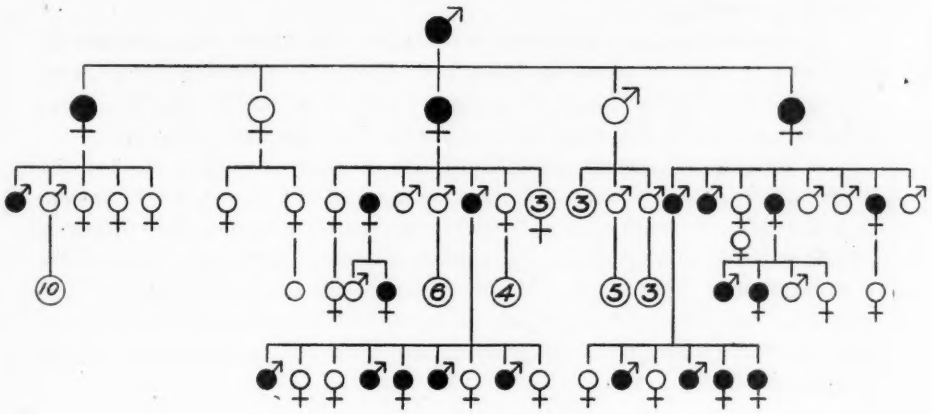


FIG. 9. *Diabetes insipidus.* Weil's family.

study of these family complaints the normal individuals are quite as important as the abnormal, and that it is advisable that as many members as possible of the family should be personally examined. The heredity in the families con-

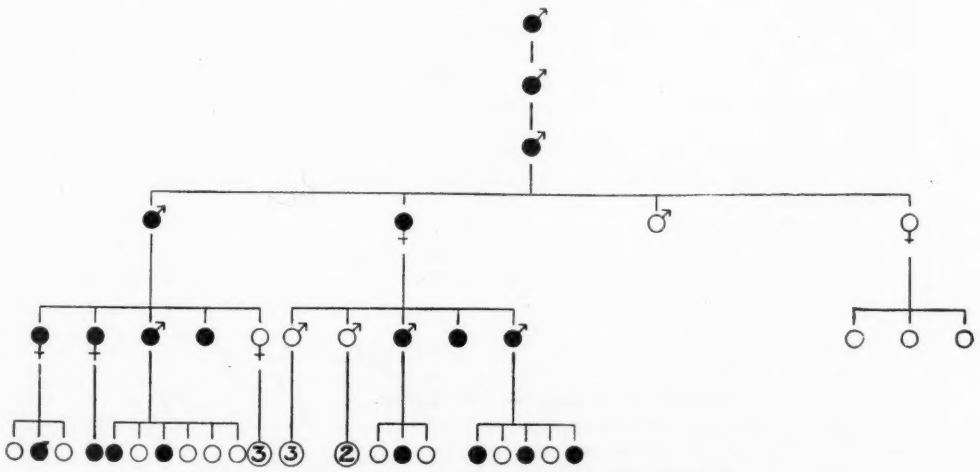


FIG. 10. *Congenital lock of white hair.* Rizzoli's family.

sidered seems to be of a comparatively simple character, the abnormal condition being dominant to the normal, but in other families one must expect a more complicated problem. For instance, the abnormality may be recessive to the

normal condition when it would be expected to show itself, especially in the offspring resulting from the marriages of cousins. Again, the condition may be limited to one sex, as appears to be partly the case with haemophilia. Accurate and full records of as many families as possible are required for the elucidation of all these problems.

In conclusion, I have to express my thanks to Dr. Colcott Fox, who greatly facilitated the task of searching through the literature by lending me his note-books, to Dr. Graham Little for getting details of a family translated from a Russian periodical, and to Mr. Bateson for constant help and criticism.

A few diagrams are appended, illustrative of family histories. In these the affected individuals are black, the normal ones white, and the sex, where known, is indicated in the usual way. The individuals are not placed in these diagrams in the order of primogeniture. A number of normal persons is indicated by a numeral in a large circle. In the references the numbers of affected and unaffected individuals in each family are given. A black spot being placed at the top of the columns of the affected, and a white one at the top of the unaffected.

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CAISSON DISEASE[1]

By A. E. BOYCOTT

Compressed air has been used for a long time to keep out the water in making tunnels, sinking shafts and the like in watery ground. A rigid metal tube or caisson is driven into the earth and filled with air compressed to the pressure necessary to keep out the water. The men excavate the earth, fix the lining of the tunnel or the foundations of the bridge, &c., as the case may be, from inside, working in the compressed air. They enter and leave the tube by a small chamber at one end provided with doors, which open on the one hand to outside air and on the other to the compressed air. This 'air-lock' is furnished with taps whereby the pressure within it is first brought to atmospheric pressure; the men then enter, close the door to air, open the cock which is in communication with the caisson, equalize the pressures in the caisson and the air-lock, and then open the other door and so enter the caisson. They leave by following the reverse process.

[1] The important literature of caisson disease is contained in, or may be readily found through, the following:—

(1) Paul Bert, *La Pression barométrique*, Paris, 1878. Full account of all the earlier literature with the classical researches of the author.

(2) E. H. Snell, *Compressed Air Illness*, London, 1896. Besides a critical account of the theories of caisson disease, gives the author's experience as medical officer of the Blackwall Tunnel.

(3) R. Heller, W. Mager, and H. von Schrötter, *Luftdruckerkrankungen*, Vienna, 1900. A monumental work of more than 1,200 pages. The abstract of previous work is very full, and an elaborate account of the caisson work at Nussdorf on the Danube is given, together with a number of animal experiments and a theoretical discussion. See also v. Schrötter, *Der Sauerstoff in der Prophylaxie und Therapie der Luftdruckerkrankungen*, Berlin, 1906.

(4) The researches of Leonard Hill and his collaborators, J. J. R. Macleod, C. Ham, and M. Greenwood, are summarized up to 1903 in the *Journal of Hygiene*, Camb., iii. 1903, 401. Their more recent work will be found in the *Proceedings of the Royal Society*, Lond., B, lxxvii. 1906, 442; lxxix. 1907, 21 and 284; *Journal of Physiology*, xxxiii. 1905, Proceedings, 6 and 7; xxxv. 1906, Proceedings, 6; *Transactions of the Junior Institution of Engineers*, Lond., xviii. 1907, 56.

(5) H. M. Vernon, 'The solubility of air in fats,' *Proceedings of the Royal Society*, Lond., B, lxxix. 1907, 366.

(6) The experiments to which personal reference is made here were carried out in 1906–7 with the aid of the large pressure chamber presented to the Lister Institute by Dr. Ludwig Mond, F.R.S., by A. E. Boycott, G. C. C. Damant, and J. S. Haldane. The animals used were chiefly goats; experiments on deep diving were also made by Lieut. Damant, R.N., and Gunner Catto. Further details of the results already obtained will be found in the *Journal of Hygiene*, Camb., viii. 1908, *Journal of Pathology and Bacteriology*, Camb., xii. 1908, and in the Report of the Admiralty Committee on Deep Diving (C. N. 1549/1907).

[Q. J. M., April, 1908.]

The other great class of workers in compressed air are divers. A diving bell is practically a caisson which is sunk bodily to the bottom and hauled up again at the completion of the work so that the men may get out. A diving dress consists of a waterproof suit of indiarubber and canvas joined round the shoulders to a rigid metal helmet and neck-piece. Air is supplied by pumps and is delivered to the helmet by a long flexible pipe. The air fills the helmet and the upper part of the dress about the chest, and escapes into the water through an adjustable valve in the side of the helmet. The pressure on this valve is the hydrostatic pressure of the depth of water between the valve and the surface; to keep up a supply of air, therefore, the air in the helmet has to be compressed to a little more than this hydrostatic pressure. The diver descends and ascends by climbing along a rope fixed to a sinker on the bottom; he is also attached to the surface by a rope which contains a telephone wire.

The terminology of air pressures is not altogether free from confusion. One atmosphere equals 760 mm. of mercury or 14·7 lb. to the square inch (commonly taken as 15 lb.), and is practically equal to one kilogram to the square centimetre, 33 feet (5½ fathoms) of sea water or 34 feet of fresh water. If pressures are specified without qualification, reference is usually intended to the readings shown on ordinary gauges—i.e. pressures in excess of atmospheric pressure. These may also be described as e.g. '+ 15 lb.' or '15 lb. positive' to distinguish them from readings in absolute pressure, i.e. the whole pressure starting with a vacuum as zero instead of atmospheric pressure. Thus +45 lb. is 4 atmospheres absolute or 3 atmospheres positive or 100 feet of sea water.

Diving work in general differs from caisson work in that in the former the men experience short exposures to high pressures, and in the latter long exposures to lower pressures. Most caissons are not worked above +30 lb. and often at less than 1½ atmospheres, though they have gone to +45 lb., and more. The shifts are usually six or eight hours at the lower and two or three hours at the higher pressures. Divers frequently descend to 20 fathoms (120 feet = +53 lb.), and not uncommonly to about 25, stopping less than half an hour at the greater depths. The deepest authenticated dives are those of Damant and Catto, who descended to the bottom in 210 feet (= +94 lb.).

It is important not to class as caisson disease all the ills from which workers in compressed air suffer. Caisson men may be poisoned by carbon monoxide or sulphuretted hydrogen, and divers by carbonic acid; both groups are obviously somewhat liable to death by violence. The illnesses occurring in men working in compressed air which are directly due to that occupation do not for the most part arise while they are under pressure but during, and especially shortly after, decompression. It is only a failure to appreciate the elementary principles of physics which has given rise to the idea that any material alterations in the circulation, respiration, &c., are produced mechanically by exposure of the whole body to increased air pressure. The pressure is transmitted instantaneously throughout the fluid mass of the tissues and equally in all directions. It is indeed not always possible, without making certain

tests, to tell from one's common sensations whether one is in air at +45 lb. or at atmospheric pressure. The only parts of the body which are directly affected by the pressure are cavities containing gas which are not in communication with the exterior. Any gas in the stomach or intestines will thus be compressed while under pressure and the surrounding parts forced in. Of more moment is the air in the middle ear. As the pressure rises this air is compressed and the membrana tympani forced inwards. The ear is exceedingly sensitive to the change, and a few strokes of the pump in the experimental pressure chamber are detected in this way long before the ordinary spring gauges move from zero. Unless the Eustachian tube is soon opened, very acute pain is produced, and the membrane may be torn or haemorrhage take place in the middle ear. It is thus difficult or impossible to go into compressed air unless the Eustachian tubes can be opened easily, either by swallowing, forcible expiration with closed mouth and nose, or—perhaps best of all—by yawning. Those unaccustomed to compressed air or with any catarrh may experience a good deal of inconvenience from this source; with practice, however, men can generally be compressed as quickly as 20 or 30 lb. a minute. If any difficulty occurs, it is of course greatest during the earlier stages of compression, when the absolute volume of air in the middle ear is changing most quickly. The opening of the Eustachian tube is valvular outwards; decompression causes no trouble, and the expanding air readily escapes into the pharynx.

The increased density of the air at high pressure may be made obvious by the impossibility of whistling owing to the fine vibrations of the lips being damped. Obstruction is felt on breathing through a tube (as in taking samples of expired air for analysis) owing to the greater viscosity of the air, and in this way the ventilation of the lungs must be to some extent impeded; there is, however, no evidence that this produces any physiological effect.

The increase of oxygen pressure in the air does not increase the respiratory exchange. It has been clearly shown by several observers that an increase of oxygen in the air breathed up to 90 % at atmospheric pressure (=air at +50 lb.) produces no alteration in the quantities of CO_2 given off or of oxygen absorbed. Hill and Macleod did not find that compressed air *per se* made any material difference in the CO_2 output of rats and mice. We found that goats gave off an average of 0·795 gms. CO_2 per kilo body-weight per hour at atmospheric pressure, 0·853 gms. at +45 lb. and 0·786 gms. at +20 to +25 lb. The mechanism of this adjustment fails with inanimate objects: tobacco is consumed furiously in compressed air, and sometimes the pipe also.

But beyond a certain limit an increase of oxygen pressure is poisonous. Bert noticed that high pressure oxygen was fatal to mammals and birds, and this observation has been fully confirmed and extended by Lorrain Smith, Hill and others. Oxygen at high pressures has a convulsant action on the central nervous system; in other instances death appears to be due to congestion of the lungs and consolidation by an exudation, which is sometimes free from cells and resembles that of pulmonary oedema, while in other cases the alveoli

contain many leucocytes, and the condition is one of acute pneumonia. The time of exposure is of importance; thus Smith found that 80% oxygen may produce pneumonia in mice in four days, 125% in three days, 180% in twenty-four hours and 300% in five hours. Roughly speaking, therefore, it may be said that 200% oxygen (or pure oxygen at +15 lb. pressure) is dangerous in a few hours. Highly compressed air causes toxic effects in proportion to the partial pressure of oxygen, hence in air the limit of safety is reached at about +130 lb. (10 atmospheres absolute or 300 feet of water). There is no evidence that exposure for a short time to 100% (= +60 lb. air pressure) or 140% (= +100 lb. air pressure) produces any ill effects.

It need hardly be mentioned that entirely different effects are produced by the exposure of different parts of the body to different pressures simultaneously. If the air pressure in the pulmonary alveoli exceeds the pressure on the surface of the body by only a few inches of water, air is liable to be forced into the circulation (as may happen during severe dyspnoea), and a corresponding diminution of intra-alveolar pressure may burst the pulmonary capillaries. These extremely dangerous conditions seldom arise in the case of men working in compressed air. Occasionally a diver may fall through the water so quickly that the air pressure in his helmet becomes less than the hydrostatic pressure on his person. The difference of pressure then tends to force his body inside the helmet and may squeeze him to death; the pressure is, however, usually only enough to cause pulmonary or conjunctival haemorrhages. Any therapeutic measures directed towards the alteration of blood pressure by the exposure of the body to a higher pressure than that of the air breathed are clearly very unsafe.

Exposure to compressed air therefore is, within the limits experienced in actual practice, in no way effective to cause illness. 'Caisson disease' is directly due to the changes brought about by decompression. It was noted long since that symptoms occurred only during or shortly after the return to atmospheric pressure, but the significance of this fact was not appreciated till Bert made his fundamental inquiries. He showed that the symptoms were due to the extra air, which had been dissolved in the body while under pressure, being given off as bubbles within the body when the pressure was suddenly reduced. No subsequent investigations have invalidated this conclusion, and nearly all observers are in full agreement with Bert, both as to the causation of the symptoms and as to his finding that if the pressure is reduced gradually the excess air finds its way out through the lungs in a natural manner by diffusion, without the formation of bubbles, and no symptoms arise.

The bubbles are given off in the fluids of the body, especially in the blood, and it may easily be imagined that symptoms of almost any kind may be seen. Such is the case. Of the more frequent symptoms, death or dyspnoea are commonly due to pulmonary air embolism, and paralysis to blocking of the vessels of the spinal cord. The commonest and least severe symptom of all (at any rate in caisson workers) consists in more or less severe pains in

and about joints known as 'bends' or 'screws'; their exact causation is not altogether settled, but it is probable that many bends are due to bubbles in the synovial fluid.

The bubbles of free gas in the blood and elsewhere contain about 82% nitrogen, 16% carbon dioxide and 2% oxygen. With air pressures up to 10 atmospheres and even higher, the tissues are able to combine with the excess of oxygen which is dissolved in the body, and which might tend to appear as bubbles on decompression. Hill and Greenwood have shown that this capacity is limited, and that oxygen (up to more than 50% of the free gas) may be liberated on decompression from high pressures of oxygen (e.g. +70 lb. oxygen = 25 atmospheres of air) if the animal shows symptoms of oxygen poisoning. It is however clear that, within the range of pressures actually experienced by men, the oxygen may be left out of account. Since respiration is so adjusted that the pressure of CO_2 within the body remains constant (and this has been confirmed by Hill and Greenwood for pressures as high as +75 lb.), the nitrogen alone has to be considered.

The circumstances and pathology of caisson disease.

The incidence of caisson disease must then depend upon (1) the amount of nitrogen dissolved in the blood and tissues of the body immediately before decompression, and (2) the opportunities which this extra nitrogen may get of escaping through the lungs by diffusion when the pressure is reduced.

1. The amount of nitrogen dissolved in the body depends upon (*a*) the height of the pressure, (*b*) the solubility of nitrogen in the substance of the body, (*c*) the extent of the means whereby the nitrogen is brought from the lungs to the tissues, or, in other words, the activity of the circulation in relation to (*d*) the duration of the exposure to high pressure.

It is clear that after an exposure of infinite duration the pressures of nitrogen inside and outside the body will become equal, and the amount of nitrogen dissolved will be proportionate to the partial pressure of nitrogen in the alveolar air. Nitrogen from air is soluble in the moist tissues and fluids of the body to the extent of 0·9 c.c. in 100 c.c. or thereby at body temperature. The body of a man of 60 kilos contains therefore about 540 c.c. of nitrogen at atmospheric pressure, when saturated after a sufficiently long exposure to air at +15 lb. 1080 c.c., at +75 lb. 3240 c.c., and so on. Hill and Ham made direct experiments on this point and obtained results as nearly concordant with theory as could be expected. That the prevalence and severity of illness after decompression depends, *caeteris paribus*, on the height of the pressure is fully confirmed both by human experience and by animal experiment. With men no symptoms occur after rapid decompression from any pressure up to +15 lb. With pressures of about +18 lb. occasional symptoms are observed, and their frequency rapidly increases as the pressure rises higher. The lowest pressure at which a human death has been recorded which was undoubtedly

due to caisson disease is +23 lb. In the caissons at Nussdorf, where the pressure eventually reached 2½ atmospheres, 3 % of the 254 cases occurred below 1½ atmospheres, and 65 % over 2 atmospheres, though the days spent at these pressures constituted 55 % and 21 % respectively of the total time of work under pressure, and the duration of decompression is stated to have been somewhat lengthened at the higher pressures. Work in caissons at +35 to +45 lb. has been found to be very dangerous unless the duration of exposure has been reduced or the time of decompression extended. The following table gives a summary of some experiments on goats which illustrate this point. It will be seen that both the frequency and the severity of illness increased with the increase of pressure although at the higher pressures the time of decompression was lengthened in order to avoid an inconvenient mortality among the animals.

TABLE I.

Pressure in lb. positive	Exposure in minutes	Decompression in minutes	No. of Goats	No symptoms	'Bends'	Severe symptoms	Death
20	240	2	22	21	1	0	0
25	240	2	23	21	2	0	0
30	60	10 uniformly	19	15	4	0	0
45	60	10 ,,	11	7	3	1	0
60	45	15 ,,	4	1	3	0	0
75	15	31 ,,	36	19	13	3	1
75	50	10 ,,	4	0	0	0	4

It has hitherto been assumed that nitrogen is soluble to practically the same degree in all the moist tissues of the body. Recent work by Vernon has however shown that fat is an important exception. He found that at body temperature fat dissolves rather more than five times as much nitrogen as blood. It follows that the amount of fat in the body has a considerable influence on the quantity of nitrogen taken up. Thus an animal with 25 % of fat takes up twice as much nitrogen as one with no fat. An average man appears to contain 15 to 20 % of fat. Taking the lower figure, the correction increases the nitrogen in the body at atmospheric pressure from 540 c.c. to 970 c.c., and at +60 lb. from 2,700 c.c. to 4,850 c.c.

The blood passing through the lungs becomes saturated with nitrogen according to the pressure of nitrogen in the alveolar air. This extra gas is carried to the tissues, and in the capillaries is shared between the blood and the extravascular tissues in proportion to their respective bulks. The partly desaturated blood then returns to the lungs, becomes resaturated with nitrogen and so on. As the tissues take up more and more nitrogen, the blood returning

from them becomes less and less desaturated till eventually the whole body, tissues and venous blood alike, are fully saturated with nitrogen, and the pressure of nitrogen in them becomes equal to that in the alveolar air. The mass of the blood in man is 5 % of the body weight; the fat in the body however increases the relative bulk of the tissues as far as their power of dissolving nitrogen is concerned, and in an average man with 15 % of fat the effective bulk of the blood is reduced in this way to $\frac{1}{35}$ instead of $\frac{1}{20}$ of the whole body, and the tissues are capable of dissolving thirty-five times as much

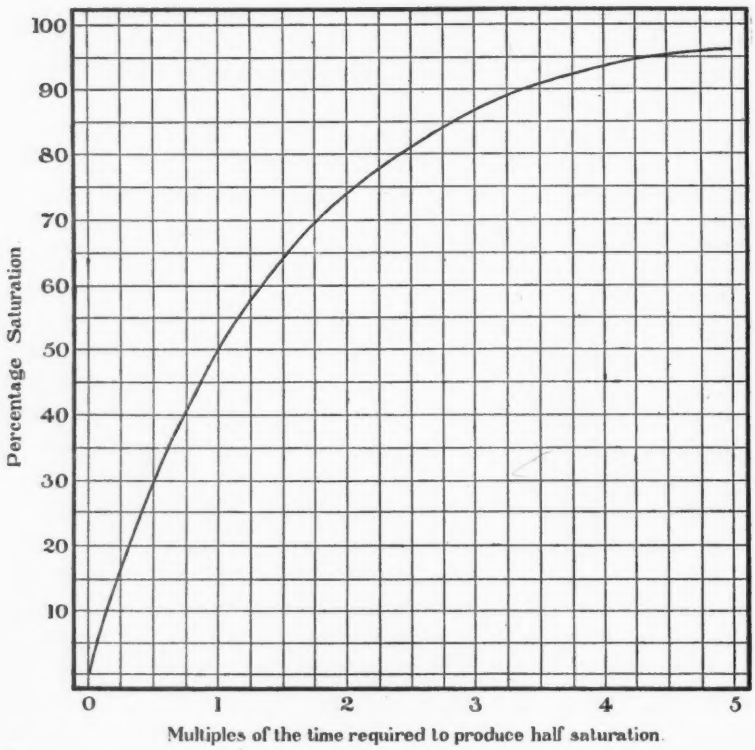

FIG. 1. Curve showing the progress of saturation of any part of the body with nitrogen after any given sudden rise of air pressure.

nitrogen as the blood alone. Assuming that the blood is evenly distributed, and circulates at an even rate, throughout the body, and that the body is suddenly exposed to an excess air pressure, the tissues will, at the end of one complete round of the circulation, have taken up $\frac{1}{35}$ of the amount of nitrogen required to saturate them completely. During the second round they will absorb $\frac{1}{35}$ of the remaining difference between their actual content in nitrogen and the amount required to fully saturate them, i.e. $\frac{1}{35}$ of $\frac{34}{35}$ of the total excess. If this calculation be followed out, it will be found that the

tissues are $\frac{1}{2}$ saturated after 23 rounds of the circulation, $\frac{3}{4}$ saturated after 46 rounds, $\frac{7}{8}$ after 69 rounds, and $\frac{15}{16}$ after 92 rounds. In other words, the nitrogen pressure in the tissues of a man exposed to +32 lb. pressure rises to 16 lb. in about twenty-five minutes, and to 30 lb. in about $1\frac{1}{2}$ hours. The general progress of the saturation of any tissue is shown in Fig. 1.

But it is quite clear that the blood is not distributed evenly to all parts of the body, and that the ratio of the volume of blood circulating per unit time to that of the tissue supplied must vary within very wide limits. In some parts, as for example glands or muscles during activity, the circulation is extremely vivacious, while in others, such as fat, it is very sluggish. It follows that the rate of saturation must be very different in different areas, and that the amount of nitrogen in different parts of the body immediately before decompression must vary in the same way unless the exposure to compressed air has been of infinite duration. It is not possible to measure the degree of saturation of most of the tissues directly. Hill and Greenwood conceived the ingenious plan of measuring the saturation of the urine secreted during profuse diuresis before, during, and after exposure to high air pressures. They found that the urine secreted after an exposure of ten to fifteen minutes to +30 or +45 lb. was fully saturated with nitrogen at the given pressure. This result may be taken as showing that the blood and kidney substance were saturated in the same short time. On the other hand, we have evidence that many parts of the body saturate much more slowly, and that these parts are of considerable importance in the causation of decompression illness. It is the experience of caisson work, even at pressures as high as +45 lb., that the men who work the air locks and are constantly being compressed and decompressed, but never stop long in the compressed air, do not suffer from caisson disease. In the same way visitors and officials who only stay in the caisson for half an hour or so show no symptoms on decompression. The only way in which the time of full saturation may be estimated under normal conditions is to observe the point at which, with increasing exposures and the same degree of pressure and rate of decompression, the symptoms cease to become any worse. The general experience of caisson workers is that a shift of eight hours is definitely more dangerous than one of four hours, and one is perhaps not very far from the mark if one assumes that a man becomes pretty fully saturated in about five hours. With regard to animals, our experiments on goats indicate that the results do not become much worse after about three hours' exposure, as shown in the next table.

This method of ascertaining the time of saturation gives, of course, only the rate at which the body takes up nitrogen which is subsequently, on decompression, effective in causing illness. The clear human experience that short exposures are not followed by symptoms, combined with Hill and Greenwood's observations, shows that saturation of the blood alone, or of very rapidly saturating parts as well, is quite unimportant in the production of illness on decompression.

2. The principles which regulate the escape of nitrogen from the body

during and after decompression are for the most part simply the reverse of those which govern saturation. If the pressure is suddenly reduced to atmospheric pressure, and no bubbles are formed, the nitrogen will be washed out from the body at a rate which is quick at first and becomes slower and slower as the nitrogen pressure in the tissues more nearly approaches that in the alveolar air (and therefore in the arterial blood). Similarly, the rate at which the different parts of the body desaturate corresponds to the rate at which they saturate. The blood desaturates every time it goes through the lungs, while areas ill supplied with blood may occupy many hours in the process.

TABLE II.

Experiments showing that the duration of exposure to high pressures is of great importance.

Pressure, 75 lb. positive, reached in 6 minutes.

Exposure in minutes	Decompression in minutes	No. of Goats	No symptoms	'Bends'	Severe symptoms	Death
1	1	6	6	0	0	0
3	1	5	4	0	1	0
6	1	6	6	0	0	0
10	1	7	6	0	1	0
15	10 uniformly	7	2	3	1	1
15	31 in stages	34	29	5	0	0
30	„ „	23	12	8	3	0
60	„ „	22	15	4	3	0
120	„ „	9	0	7	1	1
240	„ „	8	2	4	1	1

The formation of bubbles in liquids is a phenomenon which does not seem to have attracted the attention it deserves. There are certain aspects of the process which would appear to have an important bearing on the subject in hand. In the first place, a certain minimum difference of pressure of gas within and outside the liquid is necessary before bubbles are formed in a thick layer of liquid with a limited surface. What this difference of pressure must be is not precisely known; it probably varies considerably with the nature of the liquid and other circumstances to be mentioned immediately. It is doubtless correlated with the second point, which is, that very small bubbles are in a condition of unstable equilibrium and, except under very special circumstances, do not exist. It is the common experience of microscopists that none of the bubbles in their

less perfect preparations are of strictly microscopic size, and if one watches with the microscope a stream of bubbles coming off in e.g. soda-water, one sees either that no bubble at all is visible or that the bubble is quite large and can be distinguished with the naked eye. The bubbles in the blood of animals dying of caisson disease are all quite large. One can seldom make bubbles of truly microscopic dimensions by frothing liquids of any kind. We have, however, seen bubbles in treacle just visible with a $\frac{1}{6}$-inch objective which persisted for several hours. If the dissolved particles of gas which should come out of solution in order to equalize the pressures inside and outside the liquid are not sufficiently numerous and sufficiently close to one another, the time taken to form a bubble of sufficiently large size to be stable is so long that bubbling may be anticipated by the escape of the excess gas by diffusion at the free surface. The energy required to separate a bubble of free gas from a solution of a gas in a liquid is evidently considerable; very minute bubbles, or potential bubbles, coalesce to form large bubbles, and so reduce the free surface energy just as very small crystals separating from a supersaturated solution may actually redissolve and separate out again in conjunction with large crystals. The time relations are of course entirely different in the two cases; a very minute bubble either redissolves or becomes large instantaneously. In the third place, we have to bear in mind the influence of 'points' in encouraging the separation of bubbles from gaseous supersaturated solutions. If one watches the familiar tumbler of soda-water, one can generally see that, after the first rush, the bubbles come off from definite places. These are either apparently normal spots on the glass, or solid particles floating in the liquid; the latter will usually be found to be fragments of the cloth used to wipe the glass. Be it noted, too, that the stream of bubbles coming off from a bit of glass cloth in soda-water, or from a flea being boiled in xylol, does not come off indifferently anywhere, but shows a distinct tendency to arise at one end—apparently the more pointed end—of the fibre or from one particular leg as the case may be. This phenomenon of 'points' is in parallel with the familiar separation of crystals from liquid solutions on to scratches, gross or molecular, on glass surfaces, and the condensation of drops of water upon dust particles from air supersaturated with aqueous vapour. It should be especially noticed that bubbles themselves may act as 'points' on to which other bubbles are readily separated. Lastly must be mentioned the relation which blood, amniotic fluid, solution of egg-white, urine, &c., bear to dissolved gases. Any liquid may hold gas for long periods in a state of supersaturation. Simple saline solutions may, indeed, under certain circumstances hold nitrogen at a pressure twenty-five times the atmospheric pressure. As a rule the liquids of the body have a good deal greater capacity in this respect than inorganic solutions. This difference may be presumed to depend on the colloidal particles which are present. In this way a liquid, such as urine, may be highly supersaturated and yet give off no bubbles. In our experience bubbles are in fact extremely rare in the urine found in the bladders of animals dead of caisson disease, but it is quite commonly observed that the

urine passed shortly after decompression by goats which show no symptoms of illness froths freely on contact with the foreign 'points' afforded by the pavement. The amniotic fluid may show the same thing on being removed from its natural surroundings to a glass vessel. These considerations lead to the important practical conclusions that (1) a considerable time may elapse after the establishment of a large pressure difference inside and outside of a mass of body liquid before bubbles are formed, (2) the living body does not contain 'points' or at any rate not such as are very effective in causing the separation of supersaturated gas, and (3) such 'points' are provided by the first bubbles which separate.

The actual distribution of bubbles in the body after death from caisson disease is rather remarkable. None are found actually within tissue cells, and few outside the blood-vessels except in fat and in such collections of fluid as synovia and bile; in the blood they are very abundant. It is not probable that the rhythmical movements of the blood constitute a shaking efficient in disengaging the gas. The nitrogen pressure cannot be higher in the blood than in the tissues except with very short exposures which are not followed by bubbling. The only obvious explanation of why the blood bubbles so easily appears to be that it presents fewer gross mechanical obstacles to the coalescence of the dissolved gaseous particles than are found in the tissues.

These phenomena of bubbling require much further elucidation; they evidently introduce many complications into the question in hand. One of the most familiar points which probably finds its explanation here is the delay in the onset of symptoms. Symptoms may appear towards the end of the actual decompression, especially if it has been of long duration. As a rule, however, they are first seen some time afterwards. In goats 'bends' commonly appear about a quarter of an hour after reaching atmospheric pressure, and in men the onset may be still further delayed. Severe symptoms indicative of pulmonary embolism show on the whole less delay, but it is not a little curious to see a goat leap gaily from the pressure chamber after an experiment, indulge his various hearty appetites with the customary vigour and yet be dead within twenty minutes.

It will be apparent from what has already been said, that the incidence of the caisson disease, which is due to the time of decompression being too short relative to the height of the pressure and the duration of the exposure, will in the main depend on whether the nitrogen pressure within the body exceeds the nitrogen pressure outside by an amount sufficient to cause the separation of a material number of bubbles. If the pressure is reduced to atmospheric pressure instantaneously, the formation of bubbles will depend on the pressure from which the person is released: if decompression is more gradual, on whether the excess gas escapes from the body quickly enough in relation to the reduction of the air pressure to prevent the nitrogen pressures in the tissues and in the air differing by more than the minimum bubbling difference. If the excess gas in some parts of the body can escape only slowly, it is clear that the air

pressure must also be reduced slowly. The preponderating influence of the rate of decompression on the incidence of caisson disease is so well established that it need not be dealt with at length. We give only a table showing some illustrative animal experiments.

TABLE III.

Pressure, 75 lb. positive, reached in 6 minutes.

Exposure	Decompression	No. of Goats	No symptoms	'Bends'	Severe symptoms	Death
15	10 uniformly	7	2	3	1	1
15	31 „	36	19	13	3	1
15	90 „	12	9	3	0	0
30	31 in stages	23	12	8	3	0
30	68 „	14	14	0	0	0
120	31 „	9	0	7	1	1
120	92 „	19	15	3	1	0

The removal of the gas from the tissues depends on the activity of the circulation, the influence of which is well illustrated by the difference in susceptibility exhibited by different animals. The activity of the normal circulation cannot be measured directly, but in a series of ordinary mammals it is proportional to the intensity of the respiratory exchange: this is proportional to the surface, and therefore indirectly to the size, of the animal. Small animals therefore have a more active circulation than large animals. Accordingly we find that mice, weighing about 20 grammes and producing about 8 grammes of CO_2 per kilo body-weight per hour, are less susceptible than rats, weighing about 150 grammes and producing some 5 grammes CO_2 (Hill and Greenwood), rats less susceptible than goats (20 kilos and 0·8 gms. CO_2), and goats than men (60 kilos and 0·45 gms. CO_2).

The following experiment is given in illustration:—12 small rats, 12 medium rats, 8 large rats, 59 mice, 7 rabbits, 10 guinea-pigs and one old hen were raised to +75 lb. in ten minutes, left for one hour and then decompressed in 50 seconds. No goats were put in, since it had been well established in previous trials that this experience would have killed all of them. The hen and the largest rabbit (2·8 kilos) died in five minutes, and one guinea-pig in twenty minutes; all three were well bubbled. The others showed no symptoms.

Schrötter failed to produce any symptoms in dogs of about 8 or 10 kilos by sudden decompression from any pressure less than +60 lb.; abundant illnesses are caused in man, and for the matter of that in goats also, by

inappropriate release from +30 lb.; mice require at least +120 lb. to produce a material number of illnesses, while about half of an average lot of rats die after a long exposure and sudden decompression from +110 lb. With regard to the duration of decompression, Hill finds that an extension of the time from a few seconds to a few minutes will always save rats and mice: half an hour is apparently enough for dogs and monkeys from +100 lb., while goats may die after a decompression from +75 lb. lasting 100 minutes, and men after two or three hours from +60 lb. By far the most important factor in this difference is the greater activity of the circulation in the smaller animals. If this is depressed, as by anaesthetics (Hill and Greenwood), small animals become much more susceptible; small dormice, which are unaffected by a long (one hour) exposure at +120 lb. followed by sudden decompression, may be killed by a similar experiment at +75 lb. when they are in the early stages of hibernation. The most exaggerated case is presented by killing rats or mice under low pressures (e. g. +30 lb.) and decompressing the corpses quite slowly; they contain bubbles on reaching atmospheric pressure.

In the matter of the influence of the duration of the exposure, the reverse of course holds good, and small animals would be more susceptible than large ones because they become saturated more quickly. Dormice which have passed beyond the sleepy stage to deep hibernation are not more susceptible than lively dormice up to two or three hours' exposure, because they take in the excess gas so slowly.

The influence of the circulatory activity is also illustrated by the distribution of bubbles in the body after decompression. Collections of liquid such as the bile or amniotic fluid are very badly supplied with blood, and in the absence of much fresh secretion during exposure will take up gas slowly. They will also get rid of it slowly. Thus in two goats out of three exposed for fifteen minutes at +75 lb. the bile contained no bubbles, which were present in all of 8 animals exposed for one to four hours. With fifteen minutes' exposure at +75 lb. neither amniotic fluid nor foetus show any bubbles, nor does a dead foetus show any; in one hour both foetus and amniotic fluid have taken up abundant excess which, with rapid decompression, will appear post-mortem as bubbles in both foetus and fluid, but with slower decompression may be washed out of the foetus though still remaining and bubbling in the fluid. The spinal cord presents side by side areas very differently supplied with blood: Fig. 2 shows the distribution of bubbles in the cord of a goat dead of caisson disease. They are much more numerous in the white matter, which is ill supplied with blood, than in the grey matter, which has a particularly abundant circulation. In the same way the lower dorsal and upper lumbar segments, which are an inactive part of the cord and may be surmised to have the least abundant blood supply, show more bubbles than the more active lumbar enlargement where the circulation is presumably at its best. Fig. 3 shows how bubbles may be concentrated in a part of the cord in which the circulation has been brought to a standstill by blocking of the vessels by bubbles.

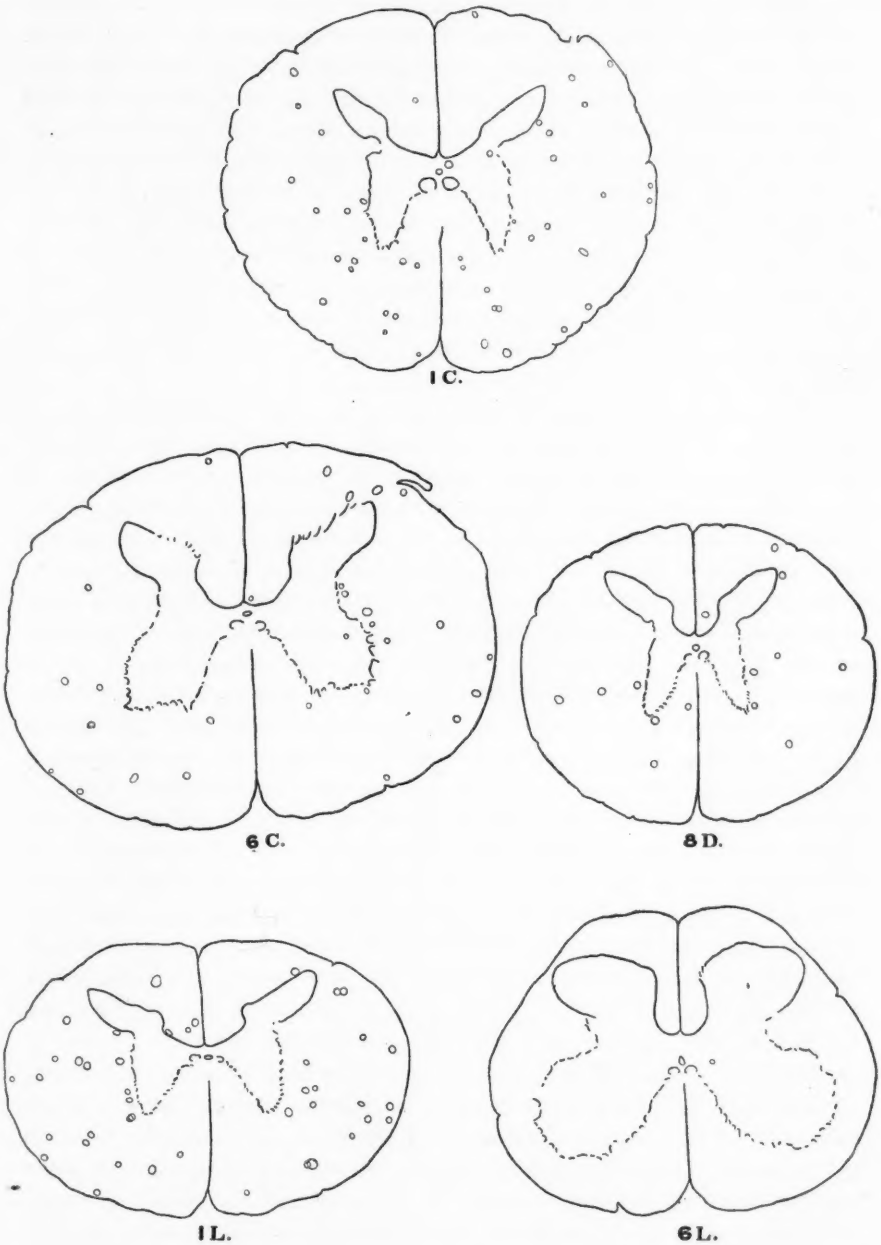

FIG. 2. Showing the preponderance of bubbles in the white as compared with the grey matter of the cord. Each diagram is a composite drawing, showing all the bubbles in 2·8 mm. length of cord. The goat was compressed to +75 lb. in 44 minutes, left 156 minutes, and decompressed in 58 seconds. It died in 12 minutes.

There are several points in the pathology of caisson disease which require further mention. Mechanical factors during decompression come into play in minor ways. Gases of fermentation accumulate in the alimentary canal while under pressure, since their volume is much diminished, and the normal stimulus for their removal is in abeyance. On decompression the abdominal distension may be extreme and may for a time materially embarrass the heart and respiration. It is somewhat surprising how seldom this occurs. A marked degree of localized pulmonary emphysema is regularly found in fatal cases in goats: this can only result from some of the smaller air tubes being impervious during decompression, an idea fully in accord with many other phenomena of pulmonary disease. This violent mechanical distension, and perhaps the rupture of capillaries from within by gaseous emboli, may cause haemorrhage in man, and small blood clots are not infrequent in the trachea in fatal cases in animals.

In connexion with gas embolism, we have to note that the bubbles are presumably for the most part set free in the venous blood. If sufficiently numerous they block the pulmonary artery. This gross pulmonary embolism is the ordinary cause of death. There is very little evidence suggesting that cardiac embarrassment plays the chief part. In some fatal cases the right heart contains very few bubbles, all the froth having been driven on into the pulmonary artery. Usually the heart contains many bubbles, but even then it continues to beat steadily and not over quickly while the animal dies of asphyxia, and continues to beat after the respiration has stopped. The mechanism of death is not necessarily quite the same as in cases where air gains entry to the circulation through a gross hole in a vein: in the latter case—and in most experiments on gas embolism—the air enters in large bullae, while in caisson disease it exists from the first as a fine froth. Despite the great mechanical difficulty of driving a froth through fine tubes such as the pulmonary capillaries, a pretty considerable quantity of bubbles passes through the lungs and is distributed by the arteries. The distribution of the infarcts arising from these emboli is remarkable. In a considerable number of goats, most of which had been through many compression experiments and had had symptoms more or less frequently, we found evidence of infarction only in fat and in the white matter of the spinal cord. This distribution, and their absence from e. g. the spleen and the kidney, suggest that the small bubbles which find their way to the arteries do not form effective emboli unless they lodge in a part surrounded by fatty material. Fat not only dissolves much more nitrogen than e. g. spleen substance, but it is a tissue particularly poorly supplied with blood. A bubble lodging among fat therefore probably finds the fat still to a large extent saturated with nitrogen and grows by accretion of this gas till it is hopelessly too large to be forced on from a place where it has very little chance of being absorbed for a long time.

The cause of paralysis is blocking of the vessels of the spinal cord. In our series of 16 cases in goats the softening has always been strictly limited to the white matter, and in 15 of the animals the condition has been a paraplegia

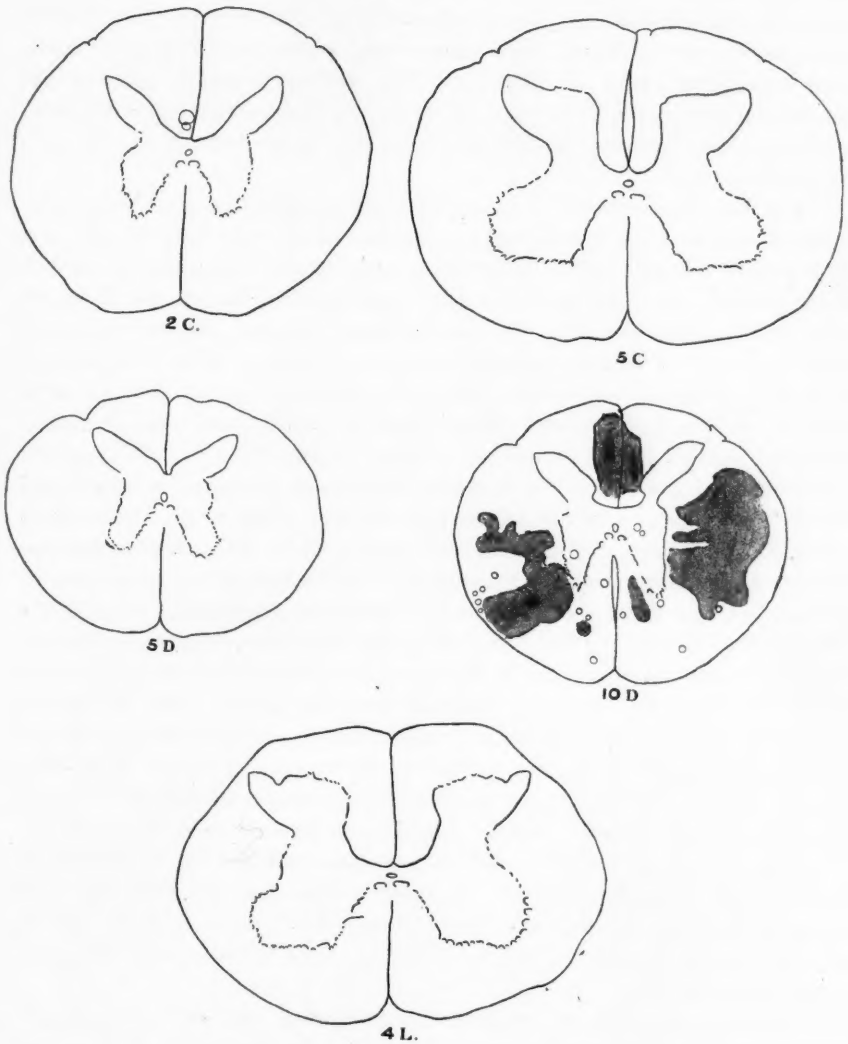

FIG. 3. Showing the concentration and persistence of bubbles in a part of the cord in which the circulation is impaired, as indicated by the occurrence of necrosis (shaded areas). The goat was compressed to +75 lb. in 6 minutes, left 10 minutes and decompressed in 48 seconds. It became paraplegic after 20 minutes and was killed 4 days later. Each section shows all the bubbles in 2·8 mm. of cord.

with the lesion localized in the lower dorsal and upper lumbar cord. The considerations already detailed appear to afford an adequate explanation of this distribution. The lesion may be of considerable extent, nearly the whole of the lateral columns and parts of the posterior columns being destroyed for a length of 4 or 5 inches. Such animals may recover and after some weeks show nothing abnormal in their gait. Fig. 4 shows a smaller necrosis and the degeneration arising therefrom. A temporary local paralysis, generally hind foot drop, which lasts from ten minutes to an hour, is common; it may leave no traces behind it in the cord.

The individual variation in susceptibility in an approximately homogeneous series of men or animals is enormous. In no caisson work have all the men been equally affected, unless all of them have escaped symptoms altogether. If for example one per cent. of the total men working die, one would expect about half to escape entirely. The same feature is always prominent in animal experiments and is very embarrassing to the investigator. Thus four goats, all males and weighing between 16·2 and 17·8 kilos, went through the same eight trials at +75 lb. pressure with various times of exposure and rates of decompression. Animal *A* had 'bends' once; *B* had 'bends' twice; *C* was paralysed three times and had 'bends' three times, while *D* was paralysed once and had 'bends' four times. One can in fact pick out individuals which are definitely susceptible from those that are relatively insusceptible. The complete explanation of this variation requires a knowledge beyond that which we at present possess, but two factors seem to be of ascertained importance. One is the activity of the respiratory exchange. Four non-susceptible goats, which between them had shown one illness in 57 decompressions, produced in two experiments 0·717 and 0·751 grammes CO_2 per kilo body-weight per hour, while four susceptible goats of rather smaller size which had been ill 26 times in 61 similar decompressions, produced only 0·624 and 0·704 grammes CO_2. The other factor is fatness. Examining the question directly, we found that in a series of 54 rats, exposed for one hour at 110 lb. and decompressed in 5 seconds, 18 which showed no symptoms had an average of 4·4% of fat, 18 which were ill 4·6%, and 18 which died 6·0%. In another series of 29 rats, those that died averaged 4·5% and the survivors 2·8%. Practical experience indicates that in men age has an important influence; this may well be due to the increasing fatness of middle life.

There is no acquired immunity to caisson disease. Animals and men may become used to slight symptoms and therefore take less notice of them, but repeated exposures do not render them any the less liable to be bubbled.

The prevention of caisson disease.

The three factors in the production of caisson disease are the degree of pressure, the length of exposure and the duration and mode of decompression. It is established that caisson disease in man would hardly occur if the pressure

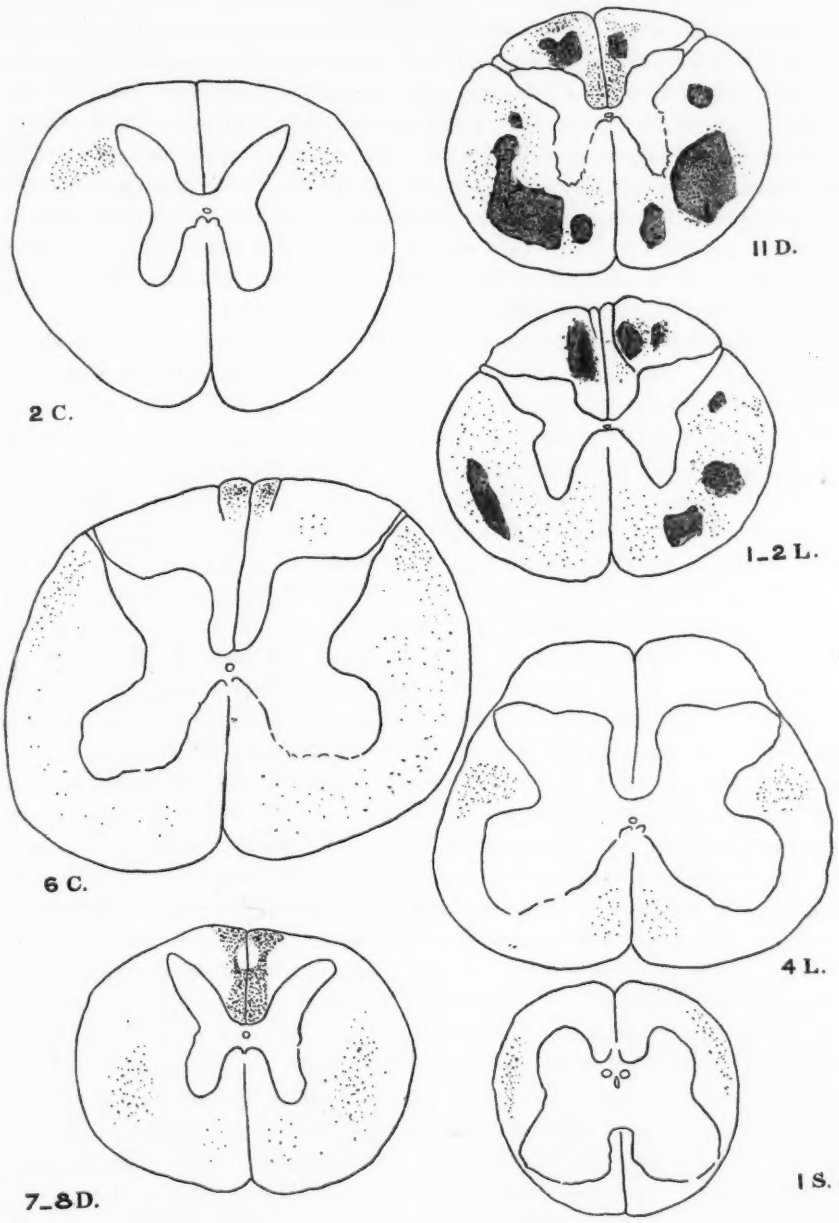

FIG. 4. Seven sections of the cord of a goat which was compressed in 40 minutes to +75 lb., left at that pressure for 30 minutes and then decompressed in 11 minutes at a uniform rate. Paraplegia ensued. Animal killed 12 days afterwards. The diagrams show the secondary degeneration (method of Marchi) from the necrosis of the white matter (shaded areas) in 10th dorsal to 2nd lumbar segments.

never exceeded +15 lb., or if the exposure at pressures up to +45 or +60 lb. never exceeded about 10 minutes, or if the decompression from pressures of the same order were never accomplished in less than five or six hours. It is equally clear that these conditions impose utterly impracticable limitations on actual work in compressed air. The problem is to allow men to work at high pressure for the longest possible time which is consistent with the total duration of decompression being kept within reasonable limits. It is especially important in diving that the duration of decompression should not be too long, since it is often not possible to be sure that conditions of weather may not render a rapid return to the surface imperative. It becomes necessary under these circumstances, therefore, to limit the duration of the exposure.

It has hitherto been customary to decompress caisson workers and divers by haphazard plans, and as a rule far too quickly. Men have been released after long exposures in caissons at +30 or +40 lb. in 10 minutes, and divers have ascended in a few minutes from depths of 20 fathoms (= +53 lb.) or more. As far as the smaller experimental animals are concerned, it has been known since the work of Bert that, if the time of decompression is prolonged to about an hour, there is no risk of any serious results. For obvious reasons this knowledge has not been acted upon in actual human practice.

It may be said at once that there is no golden rule whereby persons may without danger rapidly return to atmospheric pressure from compressed air, except by reducing the time of exposure to periods such as 15 minutes at +45 lb. or 2 minutes at +75 lb. If slow decompression has been used, it has usually been effected at a uniform steady rate: Hill has recommended a rate of 20 minutes an atmosphere. Much ingenuity has been expended on devising valves which will automatically keep the rate of decompression uniform from beginning to end. The object of this uniformity is to avoid any great difference of nitrogen pressure within and outside the body. If such difference only amounts to one or two pounds there is indeed no risk of bubble formation, but at the same time the force which is active in extracting nitrogen from the body must always be small. In consequence such a method of decompression must be extraordinarily slow: if not, the tissues which saturate and desaturate slowly will be left behind the air pressure saturated at a pressure far above the air pressure. Reasons have been already given for thinking that these slowly saturating parts are of the utmost importance, and that the quickly saturating tissues, such as the blood, may in comparison be neglected.

After exposures of reasonable practical length, then, the remedy for caisson disease would appear to be very slow decompression. Slow decompression under these circumstances cannot be avoided, but recent inquiry has shown that it may be so arranged that the necessary time may be materially reduced. The argument commences with the established proposition that *no symptoms are produced in man by quick decompressions after an exposure of any length from any pressure which does not exceed* +15 *lb.* From this we may assume that conditions of safety are satisfied, if at the end of decompression the body

is in parts left still saturated at a pressure of +15 lb. with the air pressure at +0 lb. It also appeared probable that if it were safe to reduce the pressure quickly from 2 atmospheres *absolute* to 1 (i.e. from +15 lb. to atmospheric pressure), it would be equally safe to reduce it from 4 atmospheres to 2 (+45 lb. to +15 lb.), or from 6 to 3 (+75 lb. to +30 lb.), or in general to halve the *absolute* pressure. Reduction of the absolute pressure by one-half in any part of the pressure scale doubles the volume of a gas, and may provisionally be assumed to have the same influence in exciting supersaturated solutions of gases in liquids to form bubbles, although the actual fall in pressure expressed in pounds may be very different in different parts of the scale. On subjecting the matter to experiment we found that our expectations appeared to be justified, at any rate up to a pressure of +75 lb. Some of the results are shown in the next table:—

TABLE IV.

Experiments to show that the absolute range of pressure through which decompression occurs may be of less importance than the relative range of absolute pressure.

Pressure in lb.+	Exposure in minutes	Decompression to lb.+	Actual fall of pressure in lb.	Relative reduction of absolute pressure	Duration of decompression: minutes	No. of goats	No symptoms	'Bends'	Severe symptoms	Death
75	180	24	51	5/9	4	10	10	0	0	0
51	180	0	51	3/4	4	10	2	3	3	2
45	120	−6	51	5/6	6	3	0	1	1	1
39	120	−6	45	5/6	6	4	1	0	3	0
45	120	0	45	3/4	10	12	6	4	2	0

As a matter of fact it appeared from nearly 200 experiments on the effects of a sudden drop from +75 lb. to +24 or +27 lb. that the reduction of absolute pressure may be rather more than half without any great risk to goats. From these considerations we may deduce that *the absolute air pressure can always be reduced to half the absolute pressure at which the tissues are saturated without risk of causing symptoms.*[1] Thus a man fully saturated at a pressure of +75 lb. (90 lb. absolute) may be safely decompressed quickly (i.e. in three or four minutes) to +30 lb. (45 lb. absolute), and from +45 lb. (60 lb. absolute) to +15 lb. (30 lb. absolute). Note that the difference of nitrogen pressure between the tissues and the air, which is the force which

[1] That is, up to pressures of 5 or 6 atmospheres. We have no information as to the effects of suddenly halving very high pressures.

is urging the excess nitrogen out of the body, is at first as much as 45 lb. and 30 lb. respectively in the two cases.

The *rationale* of safe, quick decompression is then (1) never to allow the nitrogen pressure in the tissues to be more than twice the air pressure, and (2) to make the fullest use of the permissible difference of pressure to get the nitrogen out of the tissues. Suppose, for example, that it is necessary to decompress a man saturated at +75 lb. He can be quickly brought to +30 lb.; nitrogen diffuses out rapidly under the stress of this drop of +45 lb., and the saturation of those of his tissues that matter falls to +65 lb. in a time which can be approximately determined by calculation according to the principles already detailed (p. 354). The absolute air pressure may now again be reduced to half the tissue pressure, i.e. to $\frac{65+15}{2} = 40$ lb. absolute or + 25 lb. The nitrogen extracting stress is now only 40 lb. at first, so that a longer wait is necessary before the tissue pressure will have fallen another 10 lb., i.e. to +55 lb. When this point is reached, the air pressure is again reduced to $\frac{55+15}{2} = 35$ lb. absolute = +20 lb., and the stress is only 30 lb. Hence the waits become longer and longer as the pressure falls. For convenience of calculation and experimentation this method of decompression is conducted in a series of steps (see Fig. 5), and is generally referred to as 'stage decompression'. Its essential peculiarity, however, lies in the fact, not that it is done *per saltus* but that it is quite quick at the beginning and very slow at the end.

The fallacies of uniform slow decompression are three in number. In the first place, no use is made of the possibility of hastening the exit of nitrogen from the tissues by putting on the greatest permissible stress. If a man saturated at +75 lb. were decompressed uniformly at the rate of twenty minutes an atmosphere, it is only at the end of about an hour that the air pressure would have reached the point to which it might have been safely brought at once; the nitrogen has been dribbling out of the tissues very slowly because the difference of pressure inside and outside the body has been so small, and much time has been wasted. In the second place, however slowly uniform decompression is conducted, the difference between the tissue pressure and the air pressure must become larger and larger; if the air pressure ever becomes much less than half the tissue pressure, it is very likely that symptoms will occur, yet the decompression goes on at the same rate and the body may reach atmospheric pressure with a tissue pressure exceeding the air pressure by much more than 15 lb. Such a rate, for example, as twenty minutes an atmosphere is quite unnecessarily slow for the earlier part of the decompression of a man saturated at +75 lbs., while it is much too fast for the later stages.[1] Uniform decompression to be safe has to be so prodigiously slow that it is an altogether irrational proceeding.

These objections to uniform decompression apply to all sorts of exposures. The third objection, namely, that the effective exposure to high pressures is

[1] The last atmosphere under these circumstances takes about two hours by the new method, and the first three atmospheres three or four minutes.

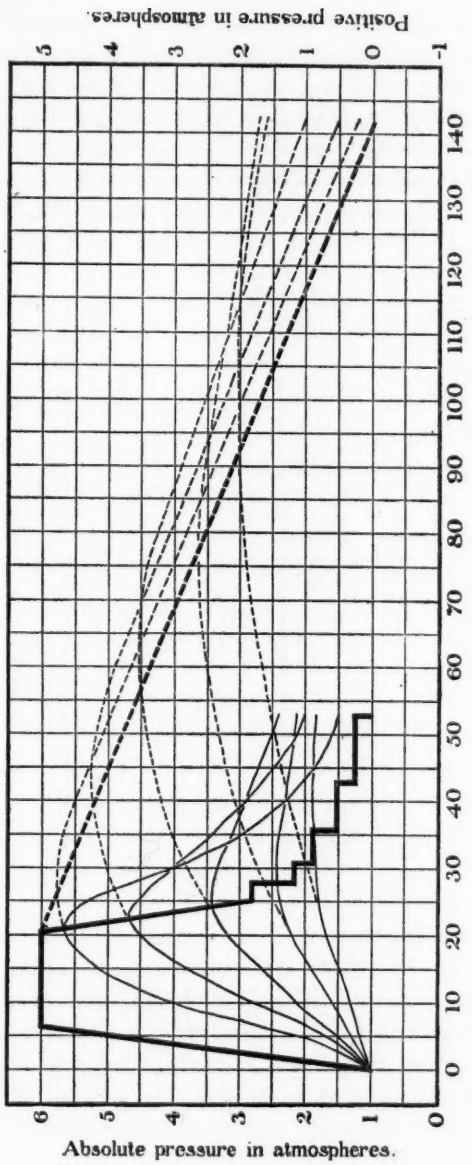

FIG. 5. Showing decompression in stages in 32 minutes and uniform decompression in 2 hours after exposure for 15 minutes at +75 lb. with compression in 6 minutes. Continuous lines = stage decompression, dotted lines = uniform decompression. Thick lines = air pressure. The thin lines represent the calculated nitrogen pressure in parts of the body which half saturate in 5, 10, 20, 40, and 75 minutes respectively from above downwards.

prolonged, only comes in, to any material extent, with exposures of short duration. If, for example, a man is exposed to +75 lb. for fifteen minutes—and this is about the maximum period of safe exposure if decompression is to be effected within a reasonable time—his slowly saturating tissues, the tissues, that is, which are of great importance in the production of symptoms, will only be saturated to a small degree; if he is rapidly brought back to +30 lb. these tissues will begin to desaturate in common with the more quickly saturating parts; if on the other hand he is slowly decompressed, they will go on taking up more nitrogen for a considerable period and will ultimately be exposed to a dangerously rapid rate of decompression. Fig. 5 shows the

TABLE V.

75 lb. positive pressure.

Series	Exposure in minutes	Decompression in minutes	Number of animals	Number of experiments	Stage Decompression				Uniform Decompression			
					No symptoms = per cent.	'Bends'	Severe symptoms	Death	No symptoms = per cent.	'Bends'	Severe symptoms	Death
A	15	31	18	34 stages 36 uniform	29 = 85%	5	0	0	19 = 53%	13	3	1
B	30	31	6	6	4 = 67	2	0	0	1 = 17	4	1	0
C	30	68	14	14	14 = 100	0	0	0	7 = 50	7	0	0
D	120	70	13	13	9 = 69	4	0	0	4 = 31	7	2	0
E	120	92 stages 100 uniform	19	19	15 = 79	3	1	0	10 = 53	3	5	1
F	180	133	10	10	8 = 80	2	0	0	5 = 50	5	0	0
			Total	96 stages 98 uniform	79 = 82%	16	1[1]	0	46 = 47%	39	11[2]	2

progress of saturation and desaturation of various tissues during and after an exposure of fifteen minutes at +75 lb. with slow uniform decompression and with decompression according to the principles detailed. It will be seen that the final result is that with uniform decompression at the rate of twenty-four minutes an atmosphere the slowly saturating tissues are saturated to the dangerous extent of about +24 lb., because the time of their exposure to high pressures has been extended. In the present example, for instance, the man undergoing uniform decompression spends 135 % more time over +60 lb., and 237 % more over +45 lb., than with the new method. .The slow descent

[1] Temporary paralysis of leg: well in an hour.

[2] Three cases of lasting paraplegia, four of temporary paralysis, two of dyspnoea, and two indefinite severe illness.

which has been recommended for divers descending to great depths is bad for the same reason.

A number of experiments were made on goats in order to compare the two methods of decompression (Table V), the total time of decompression being the same. To exclude individual variation, the same animals were, in each series, exposed to both kinds of decompression. The times and arrangement of the stage decompressions used are shown in Fig. 6. It should be noted that, except in series C and F, they were not supposed to be safe but were deliberately designed to produce some symptoms. In series E uniform decompression was slightly extended so as to investigate the supposed safe rate of twenty minutes an atmosphere.

These experiments seem to show that the method of stage decompression is essentially safe and definitely superior to uniform decompression in the same total time. It is also clear that twenty minutes an atmosphere is not always safe for goats; still less therefore is it safe under all circumstances for men who, *qua* decompression, must be more susceptible than goats roughly in proportion to the difference in their respective rates of respiratory exchange (1 to 1·7).

It is essential, if safety is to be combined with economy of time, that the times and arrangements of decompressions should be nicely adjusted to varying

TABLE VI.

Depth in feet	Pressure in lb.+	Time of exposure	Stops at different depths in minutes 70 ft.	60 ft.	50 ft.	40 ft.	30 ft.	20 ft.	10 ft.	Total time of decompression: minutes
0–36	0–16	no limit	—	—	—	—	—	—	—	1
66–72	29½–32	up to ¼ hour	—	—	—	—	—	—	2	4
		¼–½ ,,	—	—	—	—	—	3	5	10
		½–1 ,,	—	—	—	—	—	5	12	19
		1–2 ,,	—	—	—	—	—	10	20	32
		2–3 ,,	—	—	—	—	—	10	30	42
		over 3 ,,	—	—	—	—	—	20	30	52
96–108	42½–48	up to 15 mins.	—	—	—	—	—	3	5	11
		15–30 ,,	—	—	—	—	3	7	10	23
		30–40 ,,	—	—	—	—	5	10	15	33
		40–60 ,,	—	—	—	—	10	15	20	48
		1–2 hours	—	—	—	5	15	25	35	83
		over 2 hours	—	—	—	15	30	35	40	122
156–168	70–75	up to 10 mins.	—	—	—	2	3	5	5	18
		10–16 ,,	—	—	2	3	5	7	10	30
		16–30 ,,	—	—	3	5	10	15	20	56
		30–60 ,,	—	3	10	10	15	30	30	101
		over 1 hour	5	25	25	30	35	40	40	203

pressures and varying times of exposure. Calculations based on these new data and on the assumption that the slowest saturating tissues in man for which allowance has to be made are those which half saturate in seventy-five

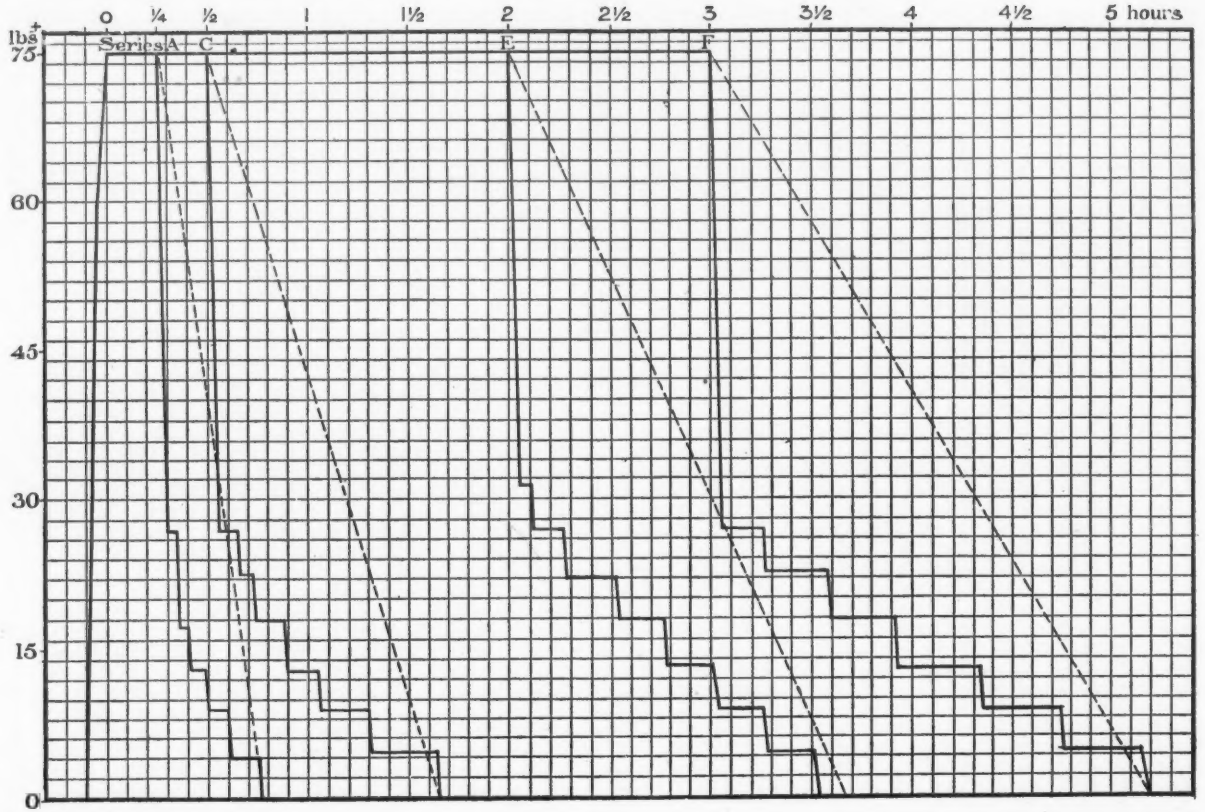

FIG. 6. Showing the decompressions used in some of the experiments given in Table V. The spacing of the stage decompressions is not so good as that subsequently devised. Continuous lines = stage decompression, interrupted lines = uniform compression.

minutes (and therefore become nine-tenths saturated in about 5 hours), have resulted in the formulation of a time-table for divers, which will be found in full in the official *Diving Manual* (Addenda, 1907). The following short extracts (Table VI) will indicate the general plan of the arrangements. In all cases the diver is to descend to the bottom as quickly as possible; the maximum ordinary time of exposure for each depth is that which allows the time of decompression to be not more than about half an hour; the ascent from the bottom to the first stopping-place is effected in two or three minutes and the subsequent ascents in about a minute each.

With regard to work in caissons, the same principles apply, though practically one has only to deal with long exposures. It is eminently desirable that the decompressions should be as simple as possible. No regulation of decompression is necessary till the pressure exceeds +15 lb. or perhaps even +18 lb. Above this up to about +40 lb. decompression could probably be done safely and simply by a quick drop to half the absolute pressure followed by slow uniform decompression at the rate of about seven or eight minutes per pound of pressure. For example, from +30 lb. the pressure is rapidly (three or four minutes) reduced to +7½ lb., and then to atmospheric pressure in an hour or a little less. This time cannot well be much cut down unless the duration of exposure is reduced: above about +40 lb. some such reduction will be necessary to prevent decompression becoming impracticably long. It is of the utmost importance that the last few pounds should not be lightly regarded and therefore hurried; a sudden drop of 4 or 5 lb. at the end may make all the difference.

The importance of the activity of the circulation should be made use of during decompression by exercising vigorously all parts of the body in order to encourage the exit of nitrogen. For the same reason it is well to diminish the air supply of a diver during the ascent and stimulate his respiration by some accumulation of CO_2. These measures would of course be improper during the earlier parts of uniform decompression after short exposures, since they would tend to increase the saturation of the slowly saturating tissues. We may note in this connexion that recent work lends no support to the view advocated by Snell that the chief factor in the causation of caisson disease is the lack of ventilation and accumulation of carbonic acid in the compressed air (Greenwood).

The last point in the prevention of caisson disease lies in the selection of the men. Practical experience indicates that young men only should be employed, and fat men should certainly be excluded. If the caisson is being worked at high pressures (e. g. +45 lb.), new hands should be tried a few times at lower pressures (+25 lb.) in order to discover and eliminate any very susceptible individuals.

The treatment of caisson disease.

The only specific treatment of caisson disease is recompression. It is most important that this should be undertaken immediately symptoms appear, so as to compress the bubbles again before they cause irreparable damage. For this purpose some small chamber supplied with compressed air should be very readily accessible; in its absence divers may be put back under water. The subsequent decompression must be conducted with the greatest caution. Bubbles once formed are not at all easily reabsorbed.

THE DIRECT INSPECTION OF THE GASTRIC MUCOUS MEMBRANE

By H. S. SOUTTAR

AND

THEODORE THOMPSON

With Plates 36–38.

I. Its Importance

The immense strides which have been made in the treatment of genito-urinary disease since the introduction of the cystoscope have led the authors to attempt the solution of the problem of the direct examination of the gastric mucous membrane. The problem in this case is of greater difficulty, but of at least equal importance. Our knowledge of the pathology of this most important secreting membrane is limited to a few gross lesions such as ulcer and carcinoma. Of the pathological anatomy of the various digestive disorders we know almost nothing, for at autopsy the mucous membrane has usually been so altered by the digestive juices that accurate investigation is impossible. And in diagnosis we are frequently at a loss to know whether a patient is suffering from a functional disorder of the mucous membrane, an ulcer, or a malignant growth.

The diagnosis of the graver disorders of the stomach has lately been the subject of research by many workers. The result of their labours has been that many of the conclusions formerly relied upon for diagnosis have been considerably modified, and, instead of becoming simpler, the subject has rather gained in complexity. The two common diseases of the stomach in which early diagnosis is imperative are carcinoma and ulcer. In many cases the failure of the present methods of examination is notorious.

In carcinoma of the stomach we have a form of new growth which remains localized to the stomach for some time, and, if the condition could be recognized in an early stage, surgical interference might lead to much more favourable results than are at present secured. Frequently the diagnosis is not made until a tumour can be palpated, and it is now known that under these circumstances secondary infection of the lymphatic glands has almost invariably occurred. Consequently it is imperative that a diagnosis be made before the tumour becomes palpable.

The physiological examination of the gastric secretion was at one time

thought likely to be of very great service. Dr. Golding Bird first noted that the secretion of HCl was greatly diminished or absent in many cases of carcinoma ventriculi. But recently many cases of gastric cancer have been published in which the amount of HCl in the test meal was either normal in amount or even increased, as in Hale White's case (*Practitioner*, Dec. 1906), and it seems probable that the absence of HCl is due rather to the accompanying gastritis than to the carcinoma itself. Thus, in an early case of carcinoma observed by the authors, HCl was absent when the patient was admitted to hospital, but under careful treatment all symptoms disappeared, and the examination of the test meals gave a normal content of HCl. The case was thought to be one of gastritis, and the patient was discharged, only to return in three months' time with an enlarged nodular liver. On post-mortem examination a small growth was found in the stomach, with secondary deposits in the liver. Moreover, the work of B. Moore and the cases investigated by Morton Palmer at Guy's Hospital have shown that carcinoma in parts of the body other than the stomach leads to a great diminution of the amount of HCl in the gastric juice. Consequently we must accept the conclusion of von Jaksch and A. E. Garrod (*Clinical Diagnosis*, p. 188), 'that the presence or absence of free HCl in cases of carcinoma of the stomach is a symptom of doubtful import, and that it must be weighed in conjunction with the other circumstances of the case.'

It is doubtful whether the other abnormalities found in test meals from cases of cancer of the stomach, such as the presence of lactic acid and of the Oppeler-Boas bacillus, are more than indications of the gastritis which is so often an accompaniment of gastric cancer.

As regards chronic gastric ulcer, the presence of profuse haematemesis in a young adult or person of middle age was formerly thought to be an important point in diagnosis. But the admirable clinical researches of Hale White and others have shown that profuse haemorrhage may occur from the gastric mucous membrane when chronic ulcer does not exist, and that this condition of gastric erosion is far commoner than was formerly thought to be the case. Moreover, even in chronic ulcer it is doubtful whether there is always an increased secretion of free HCl, as was claimed by Riegel, for Lenhartz finds that in gastric ulcer the amount of free HCl is often deficient.

This brief review of our present methods of diagnosis of gastric disease serves to show that the introduction of a method by which the gastric mucous membrane could be directly inspected may lead to as great an improvement in the treatment of disorders of the stomach as has the cystoscope in genito-urinary disease.

II. Previous Attempts

Some thirty years ago Nitze, the surgeon, drew the attention of Leiter, the instrument-maker, to the problem of inspecting through their available orifices

the various hollow organs of the body. The persistence of Nitze and the mechanical genius of Leiter resulted in the Cystoscope, while Leiter summed up the general problem in his tract, *Elektro-endoskopische Instrumente.* To appreciate their achievement we must remember that, when compared with the resources of the modern instrument-maker, the materials at their disposal were primitive. A hot platinum wire is a very different thing from a modern incandescent lamp, and the bulb in which it was contained had to be kept cool by a stream of water. Modern insulating materials were not obtainable and Jena glass was unknown. Their attempts at inspecting the stomach were less successful. The instrument they used was simply a huge cystoscope, and their experiments were limited to the cadaver. On the living the instrument was found to be impracticable.

Leiter, however, did not give up the problem, but succeeded in attracting towards it the interest of the young surgeon Mikulicz, then only at the opening of his career. Mikulicz attacked the subject with thoroughness. He felt that he was breaking new ground, and his articles in the *Wiener Medicinische Presse* are classical. He carefully discussed the anatomical and clinical aspects of the problem, and he thus enabled Leiter to construct, in 1881, an instrument by means of which a large portion of the stomach-wall could be seen in the living.

This instrument consisted of a rigid metal tube 65 cm. long and 14 mm. in diameter. The lower third of the tube was bent forward at an angle of 30° with the axis of the upper portion. The object of this bend was to enable the nose of the instrument to clear the lower part of the dorsal curve of the spine and to project into the stomach free from contact with its walls. A prism was placed at the angle. In the nosepiece were inserted an electric lamp and a reflecting prism, exactly as in the cystoscope. The rapid heating of the lamp necessitated a constant stream of water to keep it cool, and for this purpose two water-channels were provided in the wall of the tube, which also contained an air-channel for inflation and an insulated wire as one lead for the lamp. The tube itself furnished the second lead. The optical arrangement was as follows: One face of the reflecting prism formed a window in the side of the nosepiece. Light falling on this was reflected at the oblique face up the lower limb of the instrument and was immediately refracted by a lens close to the prism of short focal length. A minute image was thus formed of a comparatively large area of the stomach. The rays from this image now passed on up the short limb and were refracted by the prism at the angle so as to pass up the long limb, in which a lens of moderate focal length was placed. By means of the latter an image was formed near the upper end of the instrument, where it was examined with an eyepiece. In this way a fair area of the stomach was seen at one instant on a reduced scale.

In order to see other areas the instrument was turned about the axis of the upper limb. This movement could be carried through 180°, the nose thus pointing in extreme positions to the left or to the right. Three

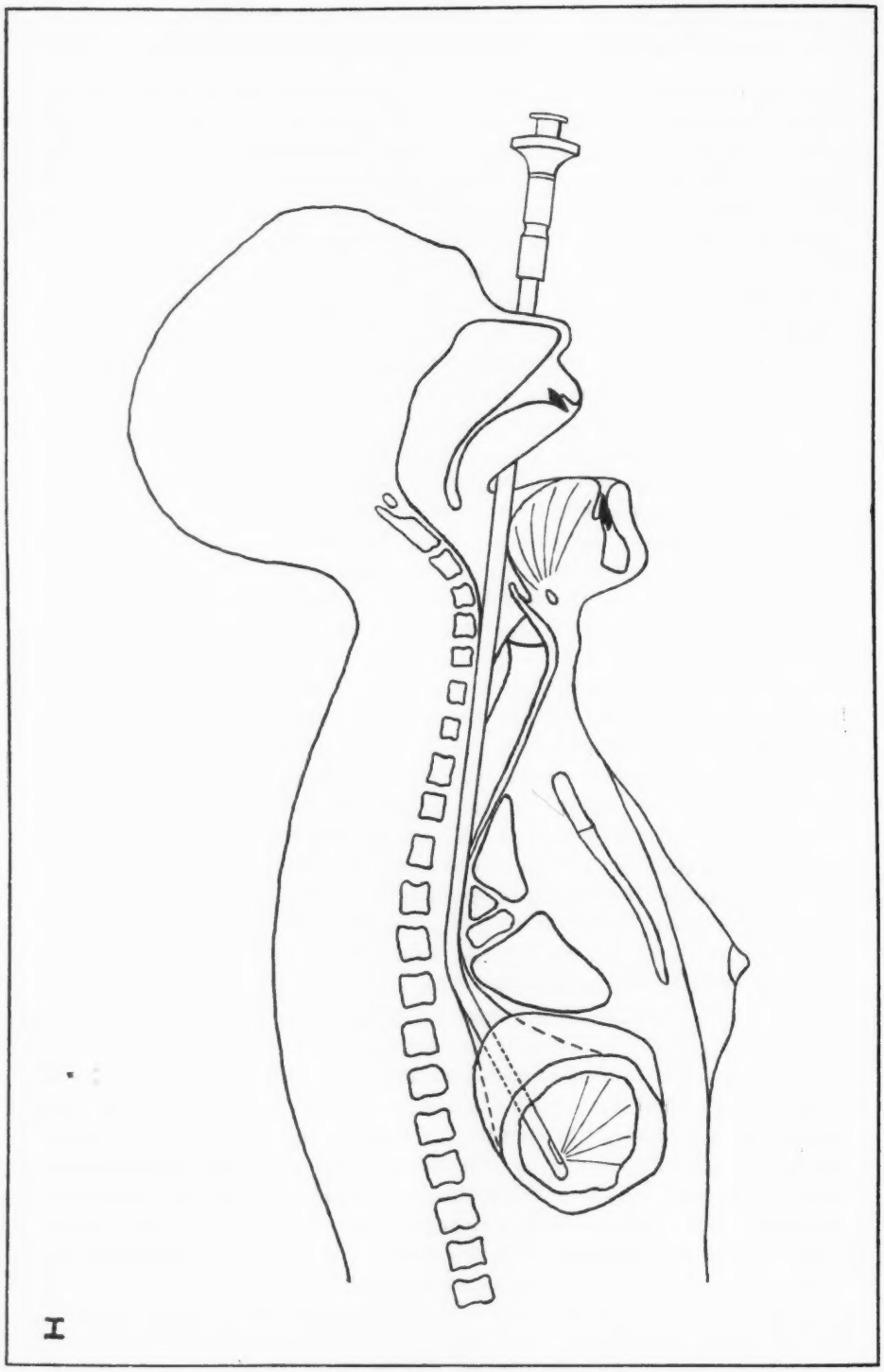

FIG. 1. The Gastroscope of Mikulicz and Leiter.

instruments were provided in which the window was placed in the front, on the left side, and on the right side of the nose respectively.

In using the instrument a very large dose of morphia was given and the patient was deeply anaesthetized, all the throat reflexes being abolished. The patient lay on his back with the head over the end of the table, or was propped up in a chair with the head tilted backwards. The instrument was introduced and the stomach inflated with air. Mikulicz himself describes the proceeding as 'an exquisite surgical manipulation which should only be undertaken by the most expert'. So far as we know, however, there were no fatalities, and he certainly succeeded in examining a number of cases. The accompanying sketch (from Mikulicz's own paper) shows the general arrangement of his instrument and its anatomical relations when in use (Fig. 1).

The instrument no doubt had many defects, to some of which Mikulicz refers. He himself deplores the absence of a rotating nosepiece. 'Unfortunately', he says, 'it is technically impossible'. But when we consider the difficulties of constructing such an instrument thirty years ago we may well do homage to the patience and the genius of Mikulicz and Leiter. Upon their instrument no material advance has been made till the present day.

In 1895 Rosenheim introduced a simpler form of apparatus, practically Mikulicz's apparatus without the bend. Except for its slight simplification the advantages of this are not easy to see. The lower end must be firmly wedged against the lower dorsal vertebrae, pinching the stomach-wall. The angle of Mikulicz's instrument enabled it to fit the dorsal curve and made it easier and safer to introduce than a straight instrument.

In 1889 Rewidzof added a flexible case to Rosenheim's instrument. The case was to be introduced first and the rigid tube passed into it.

In 1900 Kelling introduced the idea of an instrument which should be flexible during introduction and rigid afterwards. His instrument consisted of a series of tubular metal segments jointed together, so arranged that on pulling a wire shoulders on the segments butted together, the segments thus forming a single rigid tube. A similar mechanism set the nosepiece at an angle of 30° with the main axis. Thus, after the wires had been pulled taut, the instrument closely resembled that of Mikulicz and Leiter. There was one additional feature, however, for an inner tube could now be introduced into the upper limb of the instrument with gear teeth cut in its lower end. These engaged with similar teeth on an inner tube in the lower inclined limb. The nose was attached to this last tube and could be rotated by rotating the long tube introduced as above described. The whole instrument was enclosed in an elastic rubber sheath. Kelling examined a considerable number of living persons with this instrument, and apparently with some success. It was, however, costly, very complicated, and so liable to derangement that the services of an expert mechanic were constantly required. It was thus impossible that it should ever come into general use.

Finally, last year Chevalier Jackson suggested the examination of the

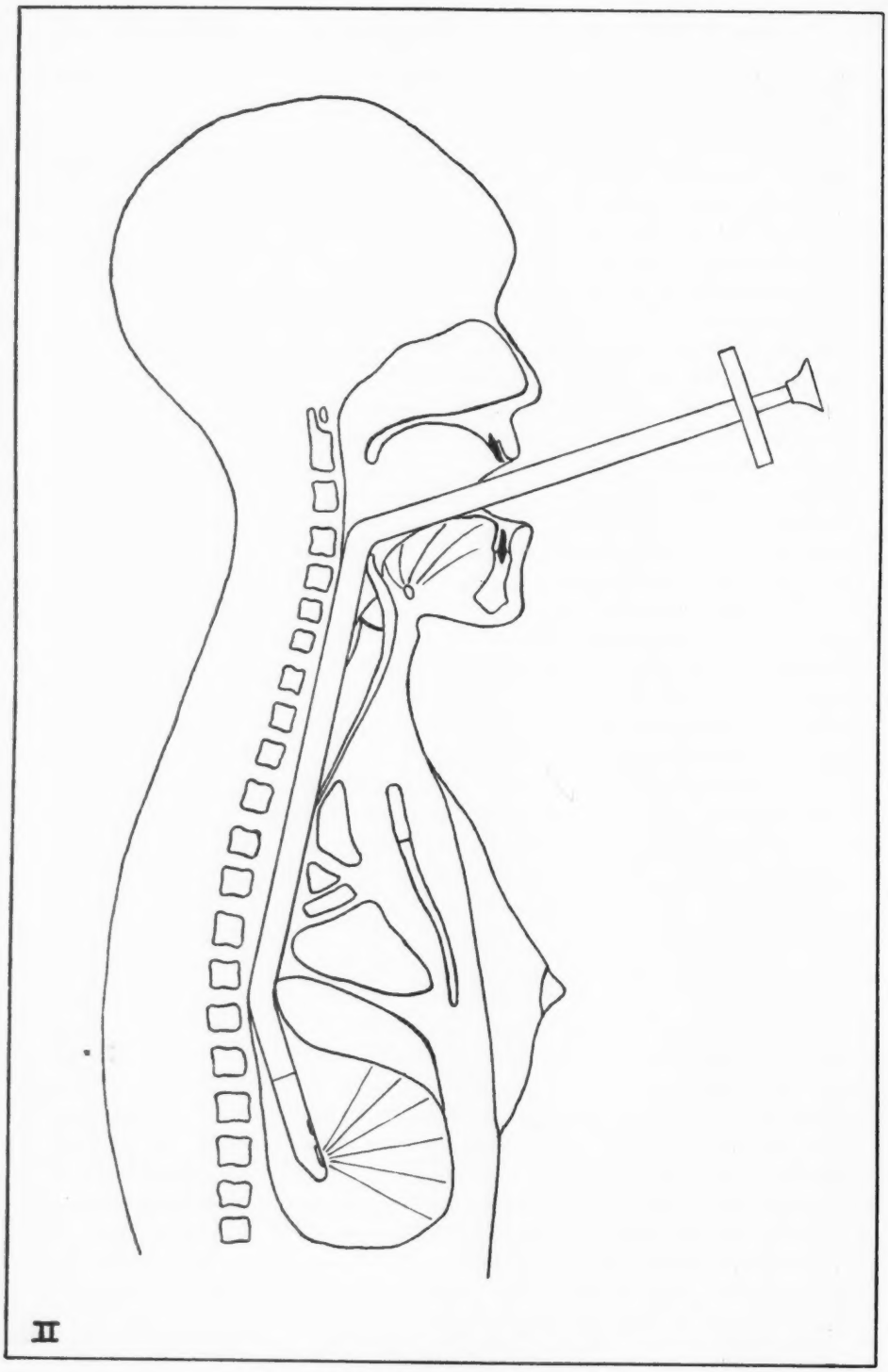

FIG. 2. The Gastroscope used by the authors.

stomach down a simple oesophagoscope tube. He did not inflate the stomach but moved the mucous membrane about by abdominal manipulation over the end of the tube. Such a method seems to involve grave risks and to be of very limited application.

III. The Problem

The construction of a satisfactory gastroscope involves many difficult problems, anatomical, mechanical, and optical. In each case the conditions are so novel that theory and analogy are of very slight assistance, and we must fall back upon direct experiment. Like any other optical instrument, a gastroscope must consist of a number of straight tubes, and at the angle between any two of these tubes there must be a prism or mirror to deflect the rays of light. Hence, the fewer the tubes and angles required the better. Remembering this, the first point to settle is the ideal form which, with the minimum number of changes of deviation, will most accurately fit the normal passage from the mouth to the stomach, while bringing the nose of the instrument well into the lumen of the distended organ.

Careful measurements on the cadaver showed us that in the erect position (or prone with the back on a suitable support) the axis of the pharynx and oesophagus from the fauces to the cardiac orifice is very nearly straight, and that the oesophagus will readily tolerate a straight rod between these points without any undue drag on surrounding structures. Such a rod, however, cannot be carried much beyond the cardiac orifice, as it will be stopped by the lower dorsal vertebrae where their bodies form the lower portion of the dorsal curve. The lower end of the rod was therefore bent forward at an angle of 30°. This brought its extremity well forward into the lumen of the stomach. An oral portion was added to the upper end, and when projecting from the mouth was found to conveniently make an angle of 120° with the oesophageal portion (Fig. 2).

We had thus laid down the general lines of an ideal gastroscope. It remained to be seen to what extent these could be realized in the living. For this purpose we passed metal-lined bougies on living subjects, and observed on a screen, by means of X-rays, their position and relations in varying positions of the individual. We then constructed a metal bougie encased in rubber, made of several short segments of metal tube so connected together that the whole formed a flexible rod, but could after introduction be straightened into the form which the cadaver showed to be best. The introduction and straightening of this were again observed by X-rays. It was found to take exactly the form intended and to cause no more inconvenience to the patient than an ordinary stomach-tube. In order to be absolutely certain on this point, the authors of this paper made themselves the first subjects of experiment.

Into the mechanical and optical problems involved we do not propose in this paper to go at any length. An instrument was constructed, consisting of

a series of short tubes strung together on two narrow steel bands, one in front and one behind. On pulling on these bands the tubes were made to butt end to end, forming a single rigid tube. Mirrors were set at the angles of this tube. The whole of this portion was encased in rubber. In the nosepiece were provided an incandescent electric lamp and a window closed by one side of a reflecting prism. A system of lenses enabled an observer to see at one time a large area, about six inches in diameter, of the stomach-wall. Finally, an extremely simple mechanical device enabled the observer to rotate the nosepiece through any angle continuously, and thus to sweep with certainty the whole stomach-wall. Means were also provided for inflating the stomach to any required degree.

In using the instrument the patient may or may not be anaesthetized. Where a tube can be tolerated the latter method offers advantages. In this case the patient sits upright on a chair, the steel bands of the instrument are relaxed, and it is passed in the flexible condition, as if it were a stomach-tube. A slight check may be experienced at the cricoid from spasm of the oesophagus. This can always be overcome by gentle pressure. The instrument will then be found to glide easily into the stomach without any pain or other disturbance whatever. After a moment's pause the patient is told to sit very erect, and the instrument will now be found to have become almost straight in its oesophageal limb. Slight traction on the steel bands makes the straightness absolute. The stomach is now inflated by means of a bicycle-pump which drives air down a channel in the instrument. The degree of inflation is checked by percussion and palpation of the abdomen. The light is now switched on and the stomach-wall brought into focus by the eyepiece. On now rotating the ebonite wheel at the eye end, the nosepiece carrying the lamp and window will rotate, thus sweeping successively all portions of the gastric mucous membrane. The only part which should escape observation is a small area round the cardiac orifice. The whole operation need take no more than two minutes. The tapes can at any instant be released and the instrument withdrawn in one second.

Under an anaesthetic the patient lies on his back with a narrow pad under his spine. The dorsal curve is thus diminished. The instrument is manipulated as before. The patient breathes easily when the instrument is in place, as it presses the tongue forward. Only light anaesthesia is required. In any case the stomach should be washed out as a preliminary.

We would lay great stress on the safety with which the instrument can be used. Of course, its passage requires care, and should always be preceded by the passage of a stomach-tube of soft rubber and of the same size. The nose passes to a carefully gauged level, and there is hence no danger to the stomach-wall as with an unmeasured bougie. The straightening is practically done by the patient himself. The release and withdrawal of the tube are instantaneous, and it is absolutely impossible that any accident could hamper or even check for an instant its withdrawal. The lamp never becomes heated.

We have had the opportunity of examining the interior of the stomach in

twelve cases. Owing to various reasons, it has not been possible to examine the whole of the mucous membrane of the stomach in all of them, but a fairly satisfactory view was in most cases obtained. In eight of the cases the mucous membrane seen had the following characters: The first appearance was that of a bright red reflex, very like that seen in ophthalmoscopic examination of the fundus oculi. On carefully focusing with the eyepiece, vessels could be seen as dark lines coursing over the field, and at times branching. Then the folds of the gastric mucous membrane could be clearly seen running transversely across the field. In these cases we assumed that the mucous membrane we had seen was normal. In the other four cases the appearances seen differed considerably. A description of these abnormal cases follows.

Case 1. W. L., 43, began in 1899 to suffer from indigestion. Shortly afterwards he began to have attacks of vomiting, and on several occasions brought up blood in considerable quantities. There were areas of both deep and superficial tenderness on the abdomen. The vomits were very acid, but the secretions in response to a test meal were normal.

In 1903 laparotomy was performed. There were no adhesions and no thickening of the stomach-wall, and on opening the organ no signs of ulcer or new growth. For four months after the operation his health was much better and he had no pain. After that time the pain and vomiting recurred.

In 1904 he had a very severe haematemesis and was ill for eight months. In 1905 he was better except for one attack of gastritis. In November, 1906, all the old symptoms returned. He frequently washed out his stomach with a tube, often with relief. In 1907 he was examined by us. The stomach was slightly dilated; there was no tenderness, superficial or deep. He was greatly relieved by bismuth and alkalies.

The stomach was examined by means of the gastroscope on several occasions. The folds of the gastric mucous membrane were clearly seen. The colour was a deeper red than normal. A few large veins were seen. No evidence of ulceration or new growth was discovered.

One one occasion he was suffering apparently from a fairly acute gastritis. On inspection the mucous membrane was much redder than usual and the vessels were engorged, small vessels coming into prominence. The membrane was so intensely sensitive that the muscular coats contracted whenever the surface was touched.

On another occasion dark purple bodies were seen lying on the surface. They proved on washing out the stomach to be the skins of damsons eaten in jam ten hours before.

Case 2. Alice G., 19, had for eight months suffered from pain coming on a few minutes after food. The pain varied in degree and she sometimes vomited

There was never any haematemesis, but she said the stools were sometimes black and tarry. She was not anaemic. There was slight epigastric tenderness. The test meal secretions were below normal.

She tolerated the gastroscope well, and an excellent view was obtained of almost the entire inner surface of the stomach. The whole mucous membrane was very pale and bloodless, the veins were small, the folds poorly marked. No ulceration could anywhere be detected.

Case 3. Thomas D., 44, had severe pains in the epigastrium and between the shoulders on September 30, 1907, and succeeding days. On October 5 he had a large haematemesis followed by melaena. He had had a similar attack twelve months before, and during the year had several paroxysmal attacks of pain, but no bleeding. Indigestion had been present for several years.

On October 5 he was admitted to Poplar Hospital. He was pale and there was localized epigastric tenderness. Later, a test meal showed that secretion of pepsin and HCl was normal.

On October 30 we examined the stomach with the gastroscope. An excellent view was obtained. The folds were well seen, but the mucous membrane appeared paler than normal. The veins were large and numerous. Extravasations of blood about half a centimetre in diameter were clearly seen beneath the mucous membrane. They were numerous and widely distributed.

Case 4. Henry C., 59, suffered from dyspepsia for fifteen years, frequently vomiting. In June, 1907, he began to have severe pain in his stomach after meals. Pain came on three hours after food and was very severe. He often vomited during an attack. He began to waste and lost two stone in three months.

In September, 1907, he was admitted to the London Hospital under Mr. Barnard. There was resistance in the epigastrium, tenderness in the pyloric area. No tumour was felt, the stomach was not dilated. We passed the gastroscope under an anaesthetic and obtained a clear view of about three-quarters of the mucous membrane. At the cardiac end it was normal, as also on the anterior surface. At the pyloric end of the greater curvature, however, a portion was seen where it had entirely different characters. Here it was devoid of vessels and folds, and appeared to be thin and tightly bound down. It was studded with slight elevations about a centimetre in diameter, as if it were pushed up by small swellings behind it.

On operation, a hard irregular tumour, probably a carcinoma, was found in the region indicated. The whole pyloric end of the stomach was buried in a mass of dense adhesions.

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DESCRIPTION OF PLATES 36-38

PLATE 36, Fig. 3. The instrument flexible, ready for introduction.

Fig. 4. The instrument straightened, as it would be after introduction.

PLATE 37, Figs. 5, 6. In process of introduction.

PLATE 38, Fig. 7. Ready for observation.

How little inconvenience the passage and retention of the instrument cause to the patient is well shown by his steadiness in each of the photographs. The exposure was in each instance about eight seconds.

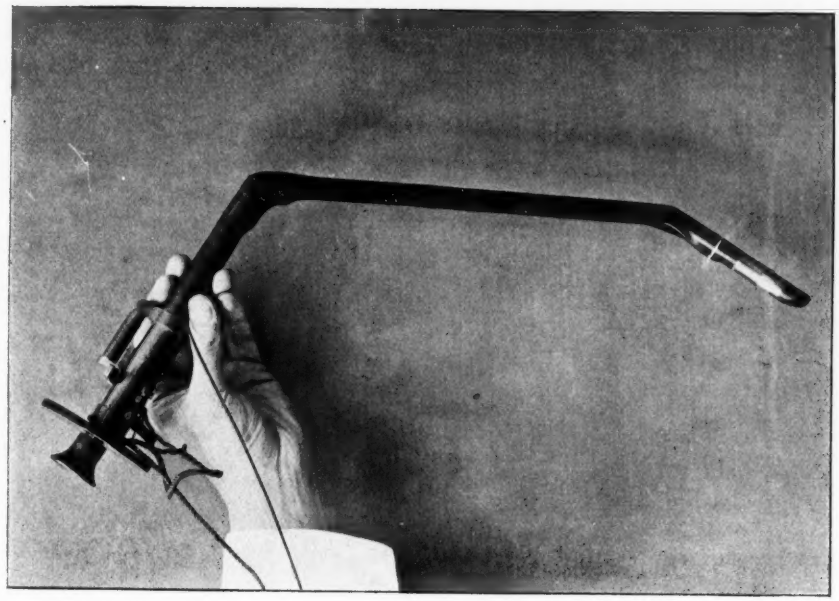

FIG. 4

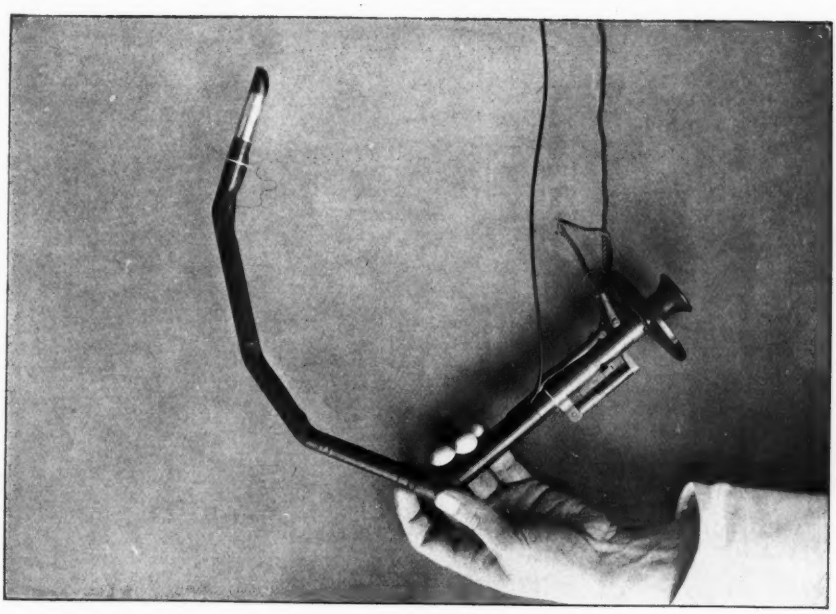

FIG. 3

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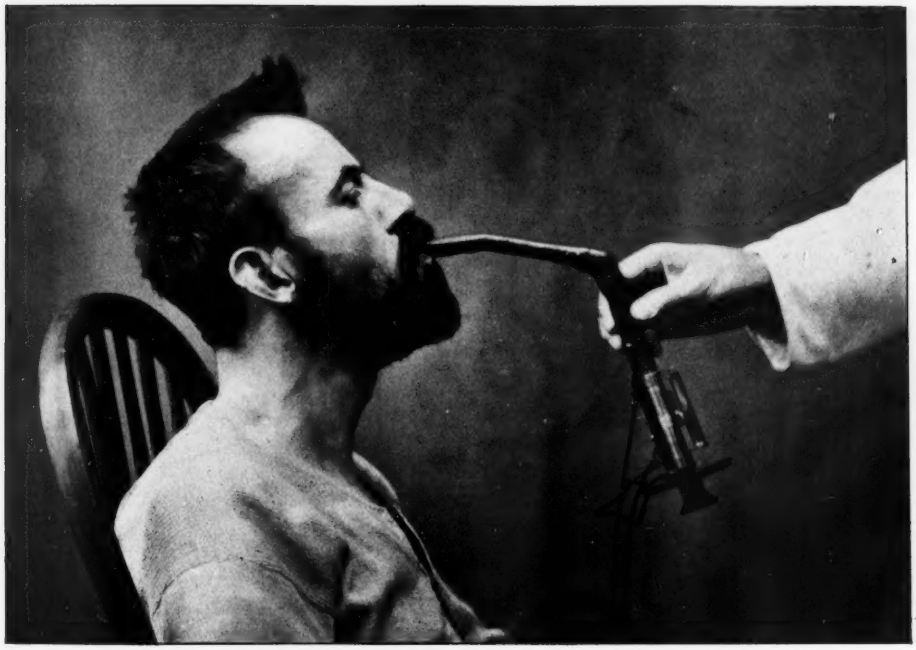

FIG. 5

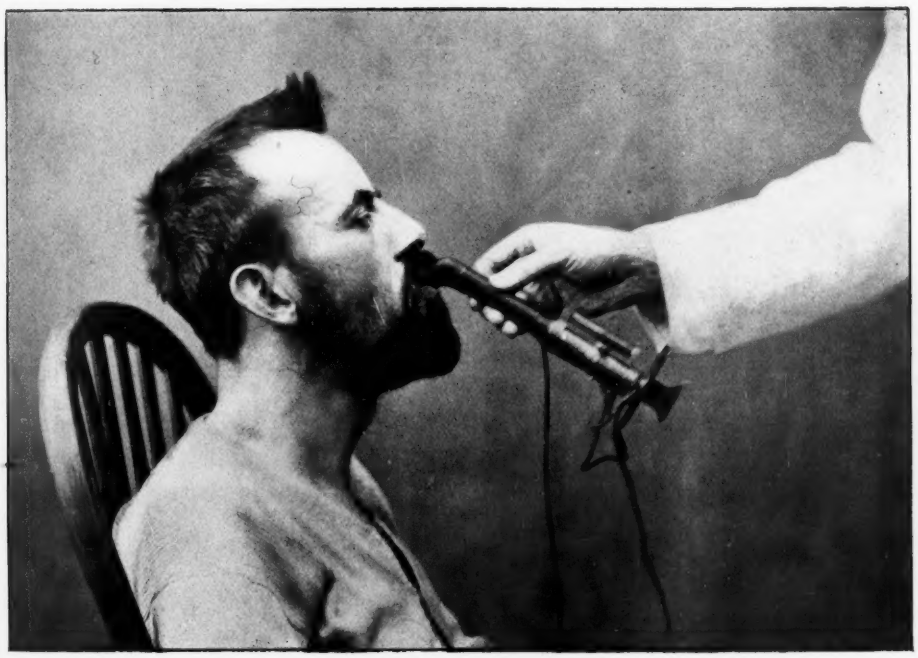

FIG. 6

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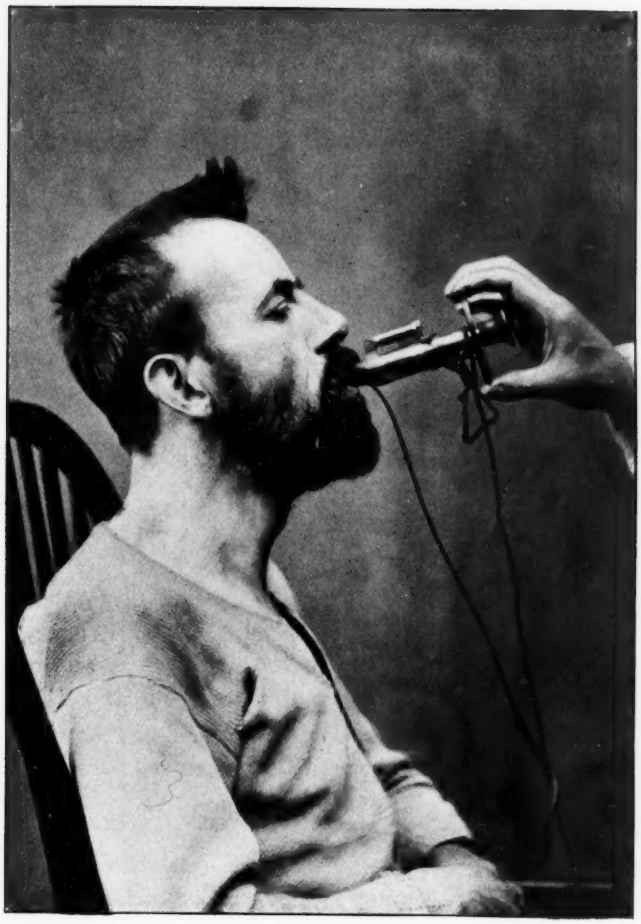
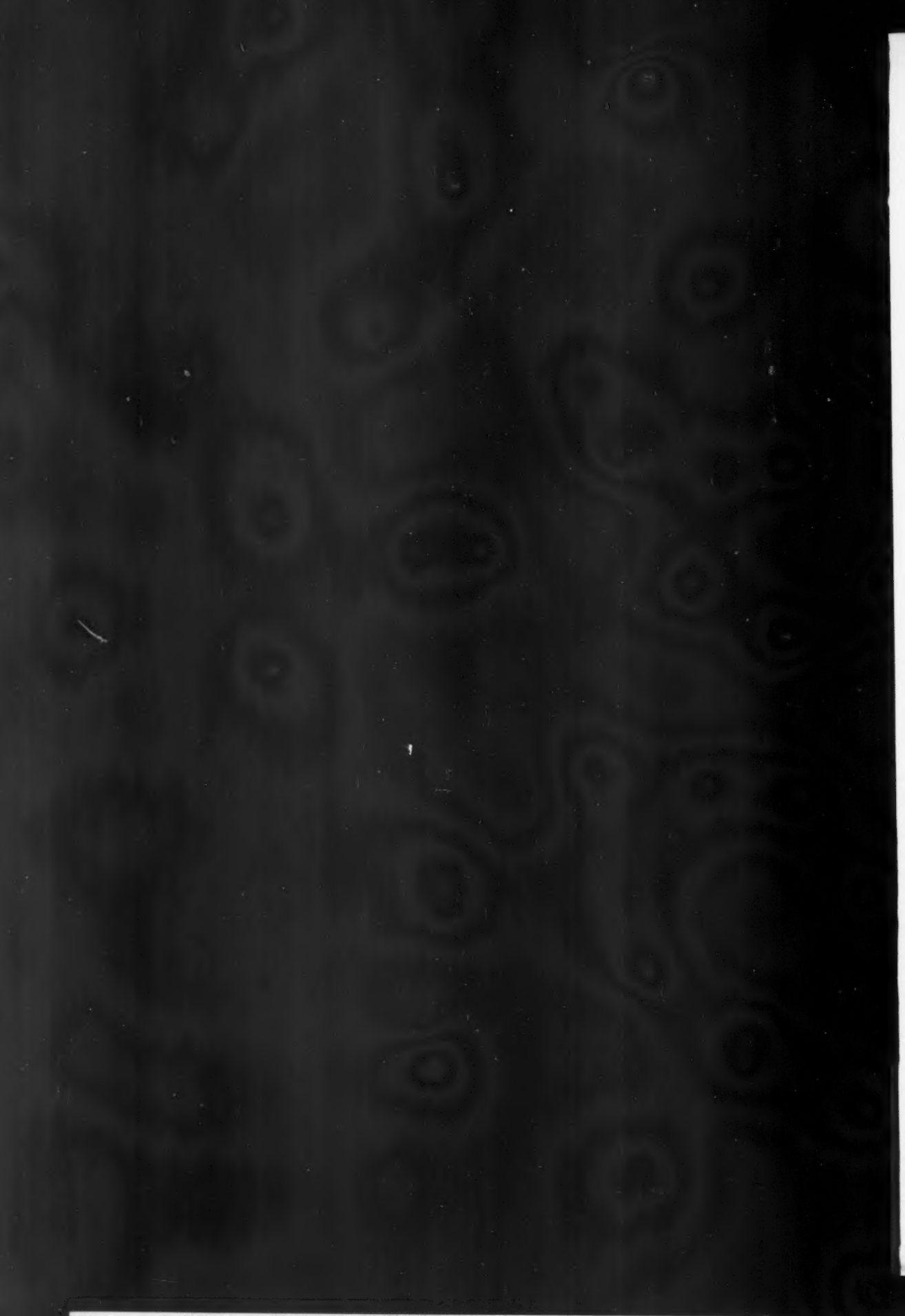


FIG. 7



THE CLINICAL BEARING OF CUTANEOUS TENDERNESS ON VARIOUS ACUTE ABDOMINAL DISORDERS, ESPECIALLY APPENDICITIS[1]

By HENRY ROBINSON

In a paper which was published in 1903, Mr. James Sherren (*a*) drew attention for the first time to the frequency of cutaneous tenderness in appendicitis, its distribution, determination, and clinical bearings. As the result of observations on 124 cases, he describes certain areas of skin connected with the terminations of the sensory nerves from the 11th dorsal segment of the cord, tenderness of which to slight stimulation, or hyperalgesia, he believes to indicate inflammation of the appendix vermiformis. More than this, Mr. Sherren concluded that in certain cases information may be afforded as to the progress of the underlying lesions.

If these conclusions are justified, it is evident that they are of great clinical importance. It is within the experience of every practising medical man that the diagnosis of appendicitis may be of considerable difficulty. Moreover, even when the diagnosis itself is not in doubt, it is often by no means easy to estimate the course which the disease is running towards resolution or the reverse. The heavy responsibility of gauging the precise moment at which surgical interference becomes the proper line of treatment would be much lighter, were it possible to make that estimation with accuracy. Every means to such an end deserves, therefore, the most careful consideration.

Dr. Head's (*a*) researches on Disturbances of Sensation, with Especial Reference to the Pain of Visceral Disease, led him to the conclusion that the intestines down to the upper part of the rectum are innervated from the 9th, 10th, 11th, and 12th dorsal segments of the spinal cord. This statement he subsequently modified by the omission of the 9th segment from the list. Dr. James Mackenzie (*a*), on the other hand, who has published several papers on the subject, assigns to the appendix and adjacent peritoneum the origins of the 11th and 12th dorsal, 1st and 2nd lumbar nerves. These researches and the rest of the literature up to 1903 are summarized in Mr. Sherren's original paper. Since that time there is but little to be found in modern works about the subject of this thesis.

Kelly and Hurdon in their monumental textbook dismiss the subject in the following summary fashion:—'Cutaneous tenderness is regarded by Blos (*Beitr. z. klin. Chir.* xxxii. 420) as a symptom of great importance.' Mr. C. B.

[1] Parts of a Thesis presented for the degree of M.D. at the University of Cambridge.

[Q. J. M., July, 1908.]

Lockwood, in his contribution to Allbutt and Rolleston's *System of Medicine*, does not even mention cutaneous tenderness throughout, nor does Sir W. H. Allchin (*a*) when dealing with Perityphlitis, nor Professor Osler in his account of Appendicitis. Presumably, therefore, these authorities have not considered the opinions put forward by Mr. Sherren; or have considered and rejected them. In either case an impartial inquiry, based upon a sufficiently large number of cases, is desirable.

For many months, while house-surgeon and house-physician, I endeavoured to test for cutaneous tenderness every case of an acute abdominal crisis which entered the wards of the hospital in which I resided. By an acute abdominal crisis was understood any condition due to, or possibly due to, acute inflammation, strangulation, peritonitis, colic, or lesions of similar urgency and severity. As a rule I did not include cases of lead colic [2], simple gastric ulcer, gastritis, and the like; though a certain number of these gained admission to my series. The series is at least an absolutely consecutive and unselected one; every accessible case was examined without bias either for or against the hypotheses which have been advanced by Mr. Sherren, and in many patients admitted by my colleagues on the resident staff I made a point of charting the areas of tender skin before obtaining any details of the history and clinical condition.

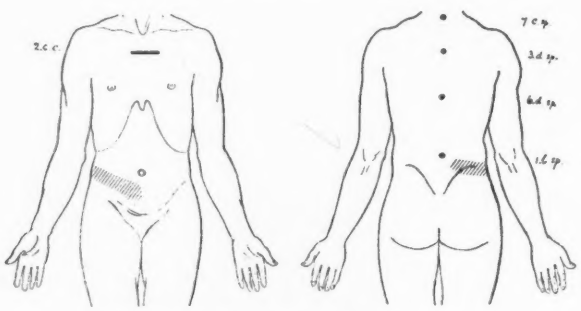


CHART 1. The Appendix Band (Sherren).

Mr. Sherren describes three main forms of cutaneous tenderness in appendicitis: he draws no distinctions between their respective significance. It is only in a proportion of cases that this symptom exists; but he holds that even its absence, as will be shown, has an important meaning in certain cases, the opposite of that assigned to its presence.

The largest area is in the form of a continuous band corresponding roughly to the distribution of the whole of the sensory fibres of the 11th right dorsal segment (Chart 1). Beginning at the back close to the mid-line, the band slopes slightly downwards as it is followed round to the front. Its lower edge just skirts the crest of the ilium, and it ends in the hypogastrium. This anterior end I have frequently found to possess a somewhat club-shaped expansion near

[2] According to Dr. Head there is no cutaneous tenderness in this disorder.

the mid-line in front, as in Chart 4, taken from my collection. I had determined this before reading Dr. Head's account of his researches, in which he also has noted what he calls the downward tag of the lower border of his subumbilical area as it approaches the mid-line in front. Another area is triangular, bounded below by Poupart's ligament, above by a line drawn out from the umbilicus, and

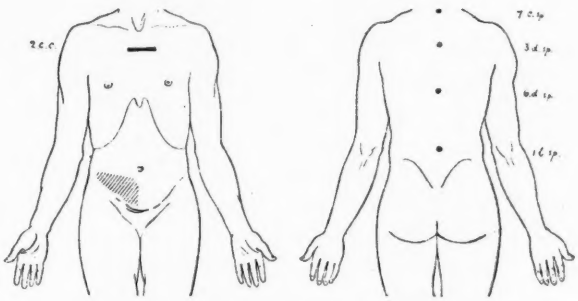


CHART 2. The Appendix Triangle (Sherren).

to the inner side by a vertical line just to the right of the mid-line. The apex of this area, which Mr. Sherren terms the appendix triangle, is at the anterior superior spine of the ilium (Chart 2). The third form is a circular patch just below the centre of the line joining the umbilicus and the spine of the ilium; with it is sometimes associated a similar area in the lumbar region just above the iliac crest (Chart 3).

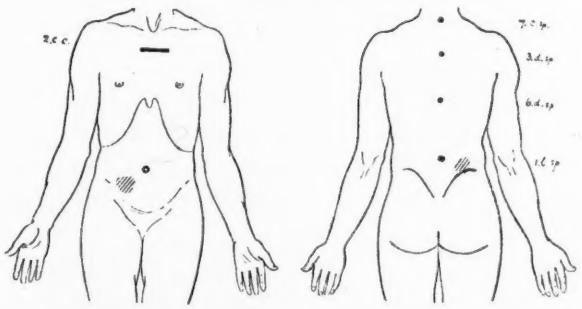


CHART 3. Circular Appendix Patches (Sherren).

With reference to these areas of tenderness Mr. Sherren has written:—

'This band corresponds to the 11th dorsal area of Head. Very often the tenderness extends somewhat into the 10th dorsal area also, and occasionally, but not often, into the 12th dorsal area, sending a tongue-like process over the gluteal region.' This tongue-like process was noticed, too, by Dr. Head, though not in association with appendicitis.

'Cutaneous tenderness in appendicitis is occasionally bilateral. I have had the opportunity of seeing two such cases, in both of which the hyperalgesia was most marked on the right side.' Dr. Mackenzie has also devoted some attention to this occasional bilateral nature of the symptoms of appendicitis. I was especially careful to search both sides, but I met with but one instance of cutaneous tenderness crossing the mid-line of the body, and then for a short distance only.

As to the aetiology of cutaneous tenderness, Mr. Sherren says: 'The cutaneous tenderness seen in appendicitis is not due to inflammation of the nerve trunks, as is sometimes seen in cases of pleurisy (Head, loc. cit.), for it may occupy the territory of the posterior primary division as well as that of the anterior primary division of the nerve.' In a later paper (*b*) he further explains: 'This superficial tenderness is due to stimulation of nerves within the appendix, the result of the tension within it.'

So much for the definition of the areas and their theoretical explanation. I turn next to their bearing on diagnosis, prognosis and treatment. I shall presently examine in detail Mr. Sherren's conclusions, and compare his statistics with my own. First of all, the following extracts from his writings may be taken to represent fairly his position :—

'I have examined all the cases of acute abdominal disease which have come under my notice in the surgical wards of the London Hospital, and have never met with cutaneous hyperalgesia in other diseases of the intestinal tract from the duodenum downwards.'

He does not, however, deny the possibility of such an event, for—

'It is anatomically possible for other portions of the lower intestinal tract to cause cutaneous hyperalgesia in a similar situation to that caused by the appendix, and Head has recorded such cases (*Brain*, vol. xvi).'

It follows quite logically from the statement already quoted, as to superficial tenderness being the result of tension within the appendix, that 'This superficial tenderness is . . . a valuable sign that the appendix is not gangrenous or perforated. It is the only sign that I know.' And also that 'Disappearance of superficial tenderness, without evidence of improvement in the general condition of the patient, calls for immediate operation'.

'It must not be considered, however, that the presence of superficial tenderness is a sign of safety. The inflammation may spread outside the appendix, and an abscess form, without leading to any diminution of the tension within it.'

'Although I consider the disappearance or absence of cutaneous hyperalgesia of great importance in deciding on operation, it is only one of the physical signs, and has to be used with the other symptoms and not apart from them. The disappearance of superficial tenderness without coincident amelioration of the symptoms indicates immediate operation, but it does not follow that operation is not urgently necessary while superficial tenderness is present, and I wish to draw special attention to this. Retention of cutaneous hyperalgesia never contraindicates operation when the general condition of the patient demands it.

'In general peritonitis arising from disease of the appendix I have never seen any superficial tenderness present. I am quite prepared, however, to meet with such a case, due to spread of the inflammation, without naked eye perforation or gangrene.'

Having now defined the propositions which it is my object to examine, I shall next deal briefly with the methods of ascertaining the presence of cutaneous tenderness. It is obviously essential that pressure shall be exerted on no structure other than the skin. The best ways are to pinch lightly very small portions of the skin with the finger-tips, and to stroke with the head of a common pin. It is advisable to start at some little distance from the usual seats of tenderness, and thence to advance gradually towards the appendix region

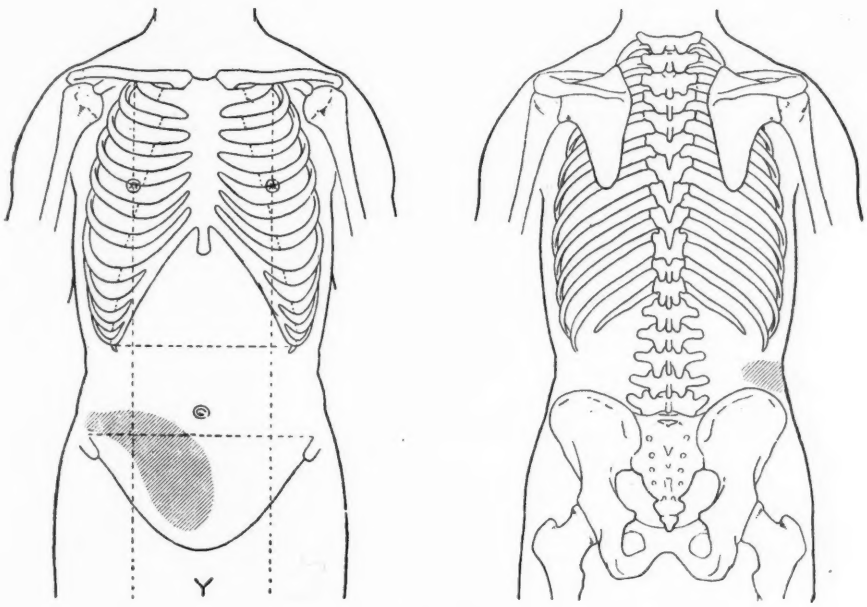


CHART 4.

until the patient complains of a sensation of pain. Besides these two plans, which have been used by Dr. Head and by Mr. Sherren, the former mentions also that of drawing a test tube full of warm water along the skin.

It may be very hard to carry out this procedure with patients whose abdomens have been treated with fomentations, poultices, or other applications which of themselves or by reason of their temperature cause tenderness of the skin. An erythema will often give evidence of such treatment, and even large blebs are not very rare. In some of these cases it is impossible to determine accurately whether there is or is not also functional cutaneous tenderness; but in many, success will attend an examination conducted with great care. Another difficulty which has been known to arise is that occasioned by the use of

carbolic acid compresses, which, owing to the local action of the drug, render the skin comparatively, and sometimes almost completely, anaesthetic.

I shall refer to those which display this cutaneous tenderness as 'positive', and to those which do not as 'negative', cases. It is remarkable in all positive cases of appendicitis how definite is the line of demarcation between the tender and the non-tender areas. Moreover, the position of each area is equally definite. The boundaries may be tested again and again to make sure that the patient is not deceiving himself and his examiner, but they will be found remarkably constant for the time being. Exceptions to this rule are extremely rare.

For the time being, as I have just said, the areas are constant. In truth they sometimes vary greatly in extent, position, and configuration at intervals

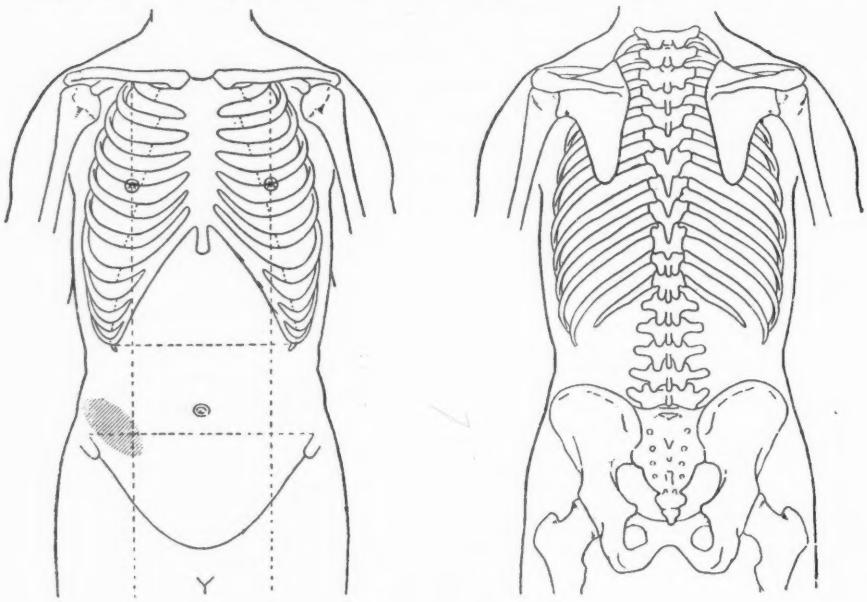


CHART 5 A.

not longer than two or three hours. Thus, Charts 5 A, 5 B, and 5 C show the areas of cutaneous tenderness on the second and third days of a mild first attack of appendicitis in a child 11 years old. On the fourth day tenderness of the skin disappeared, and the general condition was improving rapidly. There are numerous other cases in point in my series. On the other hand the patches may be found unaltered at successive examinations.

It is relevant to mention here a point raised by Sir W. H. Bennett. He refers to cutaneous tenderness as of maximum intensity in certain situations, and as diminishing gradually towards the periphery of the affected area. Though I have noted this state of affairs occasionally, in my experience it is not as a rule very prominent: at least, the margin between the hypersensitive

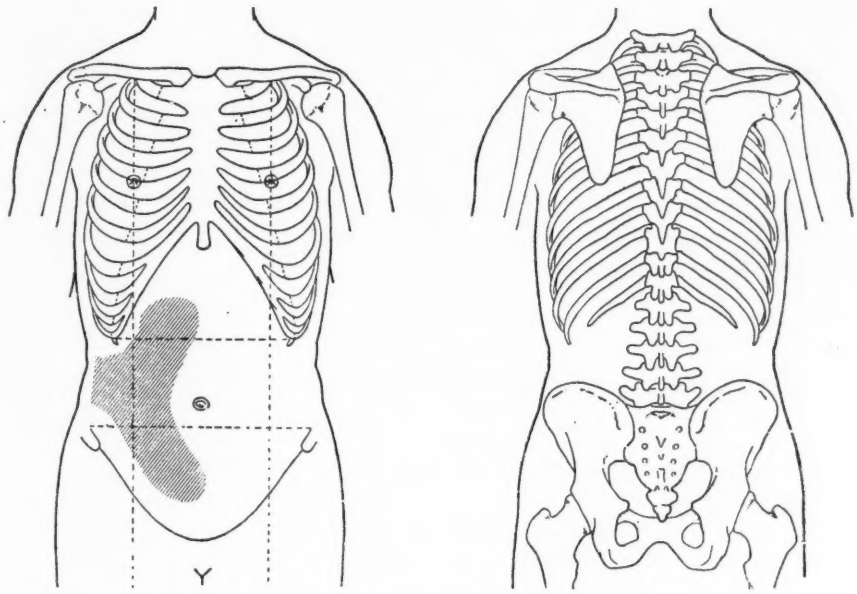


CHART 5 B.

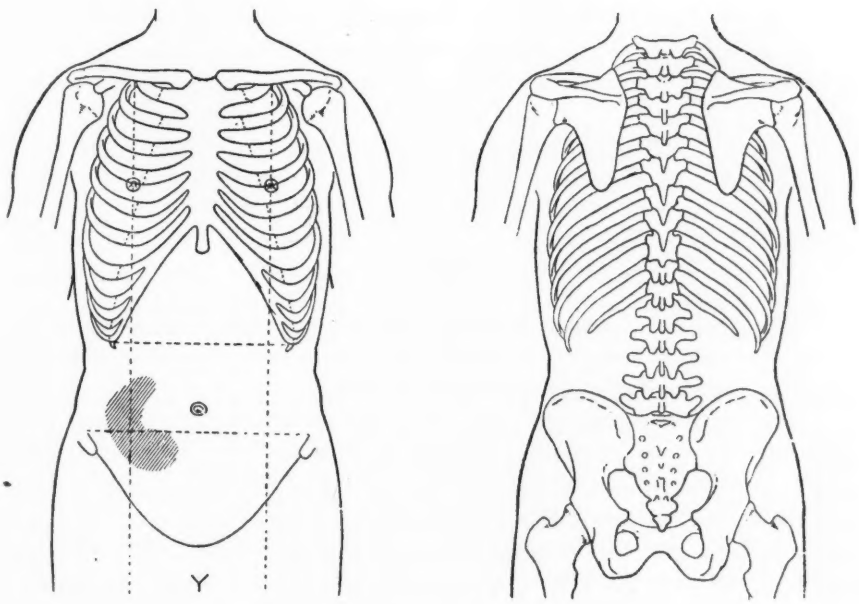


CHART 5 C.

and the surrounding skin is absolutely abrupt and defined. Two examples of Sir William Bennett's view are afforded in my collection of cases. In one, a very bad case of a large appendix abscess seen on the ninth day, there was tenderness over the greater part of the chest, abdomen, and loin, on the right side, when tested by gentle pinching; by the pin-head, however, a small circular patch was marked out corresponding exactly to Mr. Sherren's third form. In the other there was definite cutaneous tenderness in a band with a club-shaped expansion reaching nearly to the mid-line in front, and slighter tenderness over on to the left side (Chart 6). Besides these, I noted decided spots of maximum intensity in a few other cases.

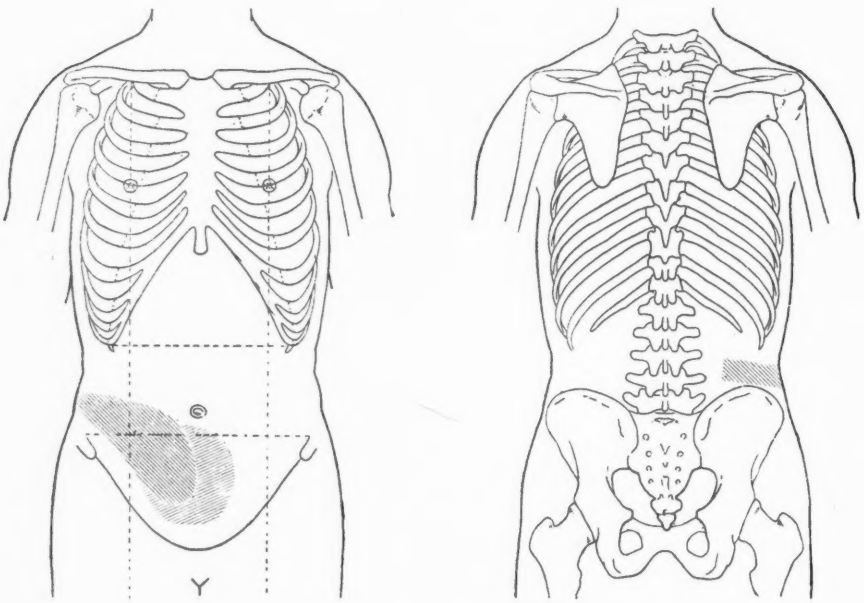


CHART 6.

With regard to Dr. Mackenzie's statements, quoted above, on the nerve supply of the appendix, it is worthy of remark that I have never seen the territory of the first or second lumbar nerves encroached upon.

Another peculiarity, which may be dwelt on here, is the tendency of a widespread area of superficial tenderness to avoid the umbilicus and its immediate neighbourhood. I am unable to explain this phenomenon, if it is in truth anything more than a coincidence (Charts 5 B and 12).

In all, I observed 123 cases of appendicitis; almost the whole of these were submitted to operation. Of other conditions I have noted 71 examples, including a few of doubtful diagnosis, some of which may have been cases of appendicitis. I shall deal first with the 123 cases of undoubted appendicitis,

and I propose to examine them with reference to the ten Conclusions adopted by Mr. Sherren at the end of his paper of 1903. These Conclusions are to be recognized by the Roman numerals prefixed to them.

I. *Cutaneous hyperalgesia is probably present at some time during all first attacks of appendicitis, except perhaps in the fulminating type, and depends on tension within the appendix.*

This Conclusion contains two distinct assertions, both of which are extremely difficult to prove or to disprove. It is not easy to understand why tension should be the only form of irritant to the afferent nerves from the appendix capable of evoking a reflex tenderness of the skin. I have notes of numerous cases in each of which a marked degree of such tenderness coexisted with a limp, rotten, gangrenous appendix, and of even more wherein appendices apparently under tension caused no such symptom. Thus, of five negative cases included in my series I find it recorded:—

'Appendix completely twisted, and of a deep plum colour; no perforation, no gangrene.'

'Tip of appendix enlarged, and full of muco-pus.'

'Appendix adherent to caecum; a few flakes of lymph on both these viscera. No perforation, no gangrene: appendix very tense, full of foul dark fluid.'

'Appendix much thickened; adhesions; dilated near tip and containing ɑ) xx of muco-pus.'

'Appendix distended with purulent fluid; no perforation, no gangrene.'

The first and third of these five were operated on during their first attacks, the second while in a chronic condition following the first attack, the fifth in the second attack, and the fourth after many attacks.

Mr. Sherren tells me that he thinks the increase of tension must take place suddenly: the dilated tip of the appendix often seen in a long-standing or chronic case is not sufficient evidence of such a rapid increase. He is also now inclined to limit his deductions to cases seen in the first attack. The third of the five examples mentioned above seems to fulfil all these conditions; for the patient's appendix was removed on the third day of an acute primary attack, and the condition of tension noted can hardly have arisen otherwise than suddenly.

In gastric ulcer it is well known that cutaneous tenderness is a frequent symptom; but there is no reason to suppose that the irritant to the afferent nerves which provokes that reflex effect is tension. Neither has any valid reason come under my notice for the assumption that tension is the only form of irritation to which the nerves of the appendix will respond in a similar way. I am not in a position to say that tension in this viscus never evokes cutaneous tenderness: indeed, I think it is at least possible that it often does. But I feel certain that tension is not the only factor, and that inflammation and the products of inflammation are capable of acting just as well; other irritants

whose possible power of eliciting reflex tenderness I see no grounds for disputing are foreign bodies, stercoliths, new growths, torsion, thrombosis and strangulation.

What it is that determines the presence or absence of cutaneous tenderness in any individual case I am not prepared to say. I have quoted cases which show that tension may exist without it, and I shall also presently describe others in which gangrene has coexisted with it; so mere destruction of the afferent nerve-fibres or endings does not seem to abolish the symptom in all cases, any more than tension on them of necessity produces it. There are other negative cases in which it might be thought that every conceivable sort of irritation was being applied to the appendix. Thus, a man aged 36, seen in his fourth

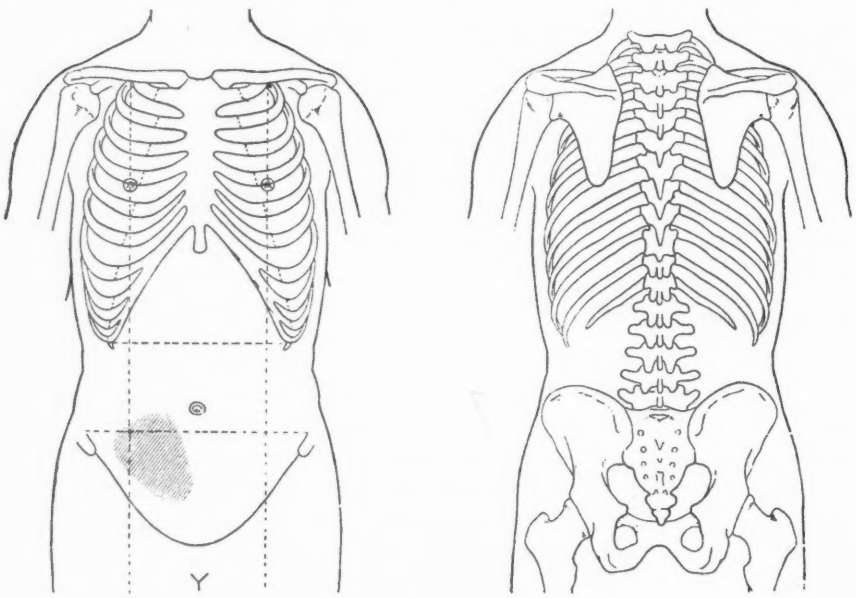


CHART 7 A.

attack, was found to have an appendix adherent to the caecum, inflamed, kinked, and the knuckle nipped in a post-caecal pouch.

Another instructive case bearing on this matter is a positive one. This patient, a girl aged 19, was first seen on the third day of an attack of abdominal pain which was diagnosed as appendicitis. She had had several previous attacks of a similar kind. There was no superficial tenderness, and the patient refused the suggested admission to hospital and possible operation. On the following day she returned worse, consented to operation if thought necessary, and was admitted at 10 a.m., when an area of cutaneous tenderness was present as shown in Chart 7 A. Observed again at 12.45 p.m. and at 8 p.m. on the same day, this area increased steadily in size (Charts 7 B and 7 C). At the laparotomy, shortly

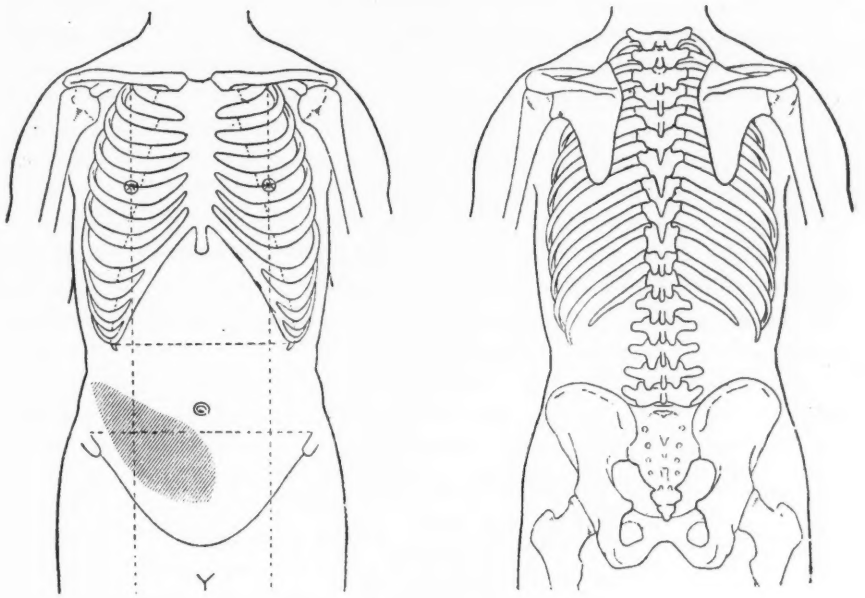


CHART 7 B.

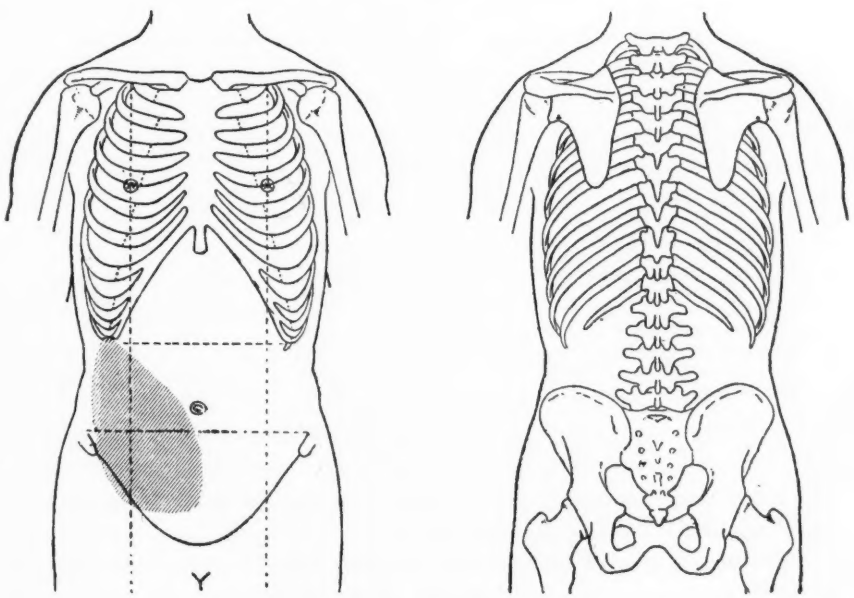


CHART 7 C.

after 8 p.m., the appendix was found adherent throughout its length to the back of the caecum: the distal ¾ inch was red and swollen, with pus visible through the coats; when examined afterwards the mucous membrane was found inflamed and ulcerated. A consideration of the history and of the findings at the operation makes it hard to believe that there was no tension in this appendix on the day before admission, and yet there was then no cutaneous tenderness.

There is evident difficulty in determining whether the first half of Mr. Sherren's Conclusion is true; not many first attacks are seen from the start, and this is especially true of hospital practice.

Among his 124 cases Mr. Sherren found hyperalgesia in 40—

6 times as a complete band,
28 „ „ an 'appendix triangle',
and 6 „ „ a circular spot,

That is, in 32·3 % of the total number.

In my series of 123 cases I find it 26 times—

10 times as a band,
4 „ „ a triangle,
8 „ „ a circular spot,
3 „ „ large irregular areas,

and once beginning as a triangle, afterwards changing to a band.

That is, in 21·1 % of the cases.

II. *It may be absent in attacks after the first, if the first attack was of sufficient severity to destroy nerve-tissue in the wall of the appendix.*

It will be seen from the subjoined table that the incidence of positive cases seems to be just as great in subsequent as in first attacks. This does not of necessity invalidate Mr. Sherren's statement, for the occurrence of previous attacks may imaginably dispose the sufferer to superficial tenderness, and so make up for the cases in which nerve-tissue has been destroyed.

	Positive cases	Negative cases	Total
No previous attack	15	62	77
One previous attack	7	19	26
Two or more previous attacks	4	14	18
Not stated	0	2	2
Totals	26	97	123

These proportions are very similar to those set forth in Table 1 of Mr. Sherren's communication to the *Lancet*.

The percentages of positive and negative cases, i.e. 21·1 and 78·9, are probably quite misleading with regard to the incidence of the symptom in private practice, in the same way as the figures of mortality would be. For it

is, broadly, the severe and the neglected cases which are seen in hospitals. Many of the milder cases, in which cutaneous tenderness is probably commoner, never reach a hospital at all; with many of those who do, it is in consequence of a progressing lesion which may have destroyed the nervous mechanism of the symptom.

III. *When present in attacks subsequent to the first, it often persists long after all other signs of the disease have gone, owing to tension within the appendix being kept up by stricture.*

I have notes of two such cases. Also of two more in which, after eleven and four attacks of appendicitis respectively, a stercolith and a fishbone were recovered from the viscus by operation. Both of these were positive cases, but unluckily I do not know whether they presented superficial tenderness during the quiescent intervals before their final attacks. It is, however, quite a fair supposition that these foreign bodies, which were sufficient to excite recurring inflammation, might stimulate the nerve-endings to the extent necessary to produce tenderness of the skin.

On the other hand, a patient in whose catarrhally inflamed appendix a threadworm was found, had no such tenderness, although the symptoms were decidedly those of appendicitis. This patient was observed in three attacks, and at no time was her case positive. Many negative cases are also recorded in my notes, in which stercoliths existed in non-perforated appendices.

IV. *It gradually disappears during convalescence as the other signs of the disease clear up.*

On this point my experience is limited, because the great majority of the cases were submitted to laparotomy before convalescence. When, however, I have had the opportunity of watching resolving cases, the areas of tenderness seemed often to assume all sorts of extensive, irregular, and migratory shapes before disappearing, as in Charts 5 A, 5 B, and 5 C.

V. *Disappearance of cutaneous hyperalgesia without improvement in the general condition of the patient is a sign of perforation or gangrene, and should be the signal for immediate operation.*

The only case in my series which bears on this point certainly supports this Conclusion.

VI. *Presence of cutaneous hyperalgesia is no contra-indication for operation. Abscesses may form and general peritonitis develop while it is still present.*

With this I am absolutely in agreement. Of my 26 positive cases,

Abscess .	.	was present in	11,	
Gangrene	.	„	„	„ 9,
Perforation	.	„	„	„ 7, and
General peritonitis		„	„	„ 3.

15 of the 26 had one or more of these complications, and the remaining 11 had not. It is possible that in one case perforation occurred during the two hours that elapsed between the clinical examination and the operation, for the symptoms became rapidly more acute, and the perforation itself seemed quite recent. This would alter the figures to 14 and 12 respectively. In his later paper Mr. Sherren (*b*) says that 'superficial tenderness is a valuable sign that the appendix is not gangrenous or perforated'. It will be seen from the statistics that the more guarded opinion, expressed in Conclusion VI, is in better accordance with the analysis of my cases. Mr. Sherren allows me to add that he still stands by both statements as the result of his increased experience since 1905.

VII. *Absence of cutaneous hyperalgesia, on the other hand, is of great importance. Absence of cutaneous hyperalgesia in a patient coming under observation early in the first attack of appendicitis is a sign of gangrene of the appendix, unless the case is obviously mild and getting rapidly well.*

Out of 62 negative cases in which there was no history of a previous attack 19 were seen in the first forty-eight hours of the disease, and 43 not until after that interval.

Of the 19 early cases there was { gangrene or abscess in 9, neither in . . 10.

Of the 43 later cases there was { gangrene or abscess in 35, neither in . . 8.

Now of the 10 early cases in which neither abscess nor gangrene was found, three certainly were 'obviously mild and getting rapidly well'; but the same cannot be said of the remaining seven. The general statement contained in Conclusion VII seems, therefore, hardly justifiable, for I find seven exceptions to it amongst 16 cases.

VIII. *Cutaneous hyperalgesia is as a rule absent in cases of abscess of the appendix.*

In my 123 cases, abscess is noted in 62, of which 11 were positive, and 51 negative. In other words, cutaneous tenderness was present in 17·7 % of all cases of appendix-abscess. Now this symptom I have found in only 21·1 % of the entire series, and even Mr. Sherren's own statistics show 10 % of exceptions to this rule, compared with 32·3 % of positive cases altogether.

IX. *The age of the patient and the position of the appendix have no influence on the cutaneous hyperalgesia.*

My observations confirm this. On the question of sex some remarks will be found on p. 408.

X. *Cutaneous hyperalgesia is occasionally of use in the diagnosis of appendicitis.*

This statement appears to be justified by an examination of the statistics. A doubtful case of intra-abdominal disease, which is found to present superficial tenderness of one of the kinds described by Mr. Sherren, will nearly always turn out to be one of appendicitis. Amongst 16 cases of acute abdominal disorder, other than appendicitis, which were positive, I find two only of the first of Mr. Sherren's forms. Each of these exactly counterfeited the appendix band; one was a case of perforated duodenal ulcer, the other of intestinal colic due to a surfeit of currants. The appendix removed by operation from the latter was quite normal. Besides these, two patients suffering from right-sided perimetritis exhibited at first the small circular patch of tenderness of the third kind.

These cases detract somewhat from the value of cutaneous hypersensitiveness in the diagnosis of appendicitis;[3] but there can be no question that the great majority of patients in whom areas of the nature described are found, do turn out to be suffering from undoubted appendicitis.

There remain one or two more paragraphs of Mr. Sherren's paper upon which my investigations throw some light. Thus he says:—

'Out of 51 cases of localized abscess of the appendix that I have examined, in 5 only was superficial tenderness present, and these were with two exceptions before the fifth day.'

This is to some extent covered by Conclusion VIII, but goes rather further, and allows me to make a more detailed examination of my own statistics upon the point. I have 11 instances of superficial tenderness in 62 of localized abscess. In two of these cases, both of them positive, general peritonitis afterwards developed, though the abscesses were noted at the time of operation as localized. Of the 11,

2 were seen on the second day (one of these developed general peritonitis),
2 „ „ third „
1 „ „ fourth „
2 „ „ fifth „
1 „ „ sixth „ (developed general peritonitis),
1 „ „ ninth „
1 „ „ twelfth „ and
1 „ „ twenty-second day.

The 51 negative cases of localized abscess were all seen, with one exception, on the seventh or subsequent days, the majority after the ninth. It is, therefore, evident that when this combination of abscess and cutaneous tenderness does occur, it is in early cases, or, at least, in earlier cases than those in which abscess without tenderness is encountered.

[3] Cf. also Dr. Head's cases of renal colic, prostatitis, and strangulated hernia, loc. cit. (*a*).

Another of Mr. Sherren's statements is :—

'In cases such as those coming under observation usually about the third or fourth day, with the signs of appendicitis well marked, I consider absence of hyperalgesia the determining factor in operation. In over 20 cases of early appendicitis without cutaneous hyperalgesia on which I have operated, I have found perforation or gangrene without exception.'

I have examined all the negative cases seen during the first four days of the illness, and, even after excluding several which were 'obviously mild and getting rapidly well', I find 12 of them showed neither perforation, gangrene, nor abscess, compared with 16 in which one or more of those complications existed. Mr. Sherren tells me that by an acute case, or one 'with the signs of appendicitis well marked', he means a grave emergency in which instant operation is imperatively demanded: whereas I have considered all cases seen during an attack. It is, however, obvious that if the definition of an acute case is to be thus restricted, there is little need of an additional indication for operation, and that there are sufficient 'determining factors' without the absence of hyperalgesia.

The last proposition which invites comment is :—

'In general peritonitis arising from disease of the appendix I have never seen any superficial tenderness. I am quite prepared, however, to meet with such a case due to spread of the inflammation from the appendix without naked eye gangrene or perforation.'

I have had an opportunity of seeing the coincidence which Mr. Sherren forecasts. The patient was a woman with the most widespread and, apparently, acute septic peritonitis which I have ever seen, and she had when admitted a small circular patch of cutaneous tenderness. Although the case was regarded as hopeless when the operation revealed the condition of the peritoneum, the patient recovered. The appendix was found to be inflamed, but not visibly perforated or gangrenous.

This question of the coexistence of superficial tenderness with general peritonitis is one upon which opinion seems to be much divided. Sir F. Treves (*a*) twice refers to the phenomenon. Thus he writes :

'A cold hand is laid upon the abdomen, or a blow upon the part is threatened, and the muscles of the belly wall become rigid in a moment; or it may be that there is some sudden lesion of the peritoneum or of one of the abdominal viscera, and at once the muscles of the belly wall contract, and a more or less marked hyperaesthesia of the skin develops, and there is thus provided, by the tender integument and by the rigid muscles, that protection and that securing of rest which are the first elements in the natural treatment of a damaged part.'

Again, speaking of general peritonitis (*b*), he says :—

'When the peritonitis is well established . . . there is very considerable tenderness' (of the abdominal walls) 'to the touch, which depends mainly on hyperaesthesia of the skin'.

Similarly Dr. Hale White (*a*) holds that 'the skin is often hyperaesthetic' in general peritonitis, and alludes to the point again in the discussion of the

differential diagnosis between peritonitis and intestinal obstruction, lead colic, and so forth.

Sir W. H. Bennett goes further still, for he assigns to the peritoneum the responsibility for the initiation of the whole process of reflex cutaneous tenderness. In the clinical lecture already quoted he says :—

'In the development of this hyperaesthesia it is essential that the peritoneum or pleura should be involved; it is, for instance, never met with in abscess in the liver, in the lung, or in the spleen in the absence of peritonitis or pleurisy. So far as appendicitis is concerned the occurrence of acute hyperaesthesia of the abdominal wall may be generally regarded as indicative of surgical complications; for example, grave appendix disease, probably with impending gangrene, subphrenic abscess, or empyema, according to the situation of the point of intensity.'

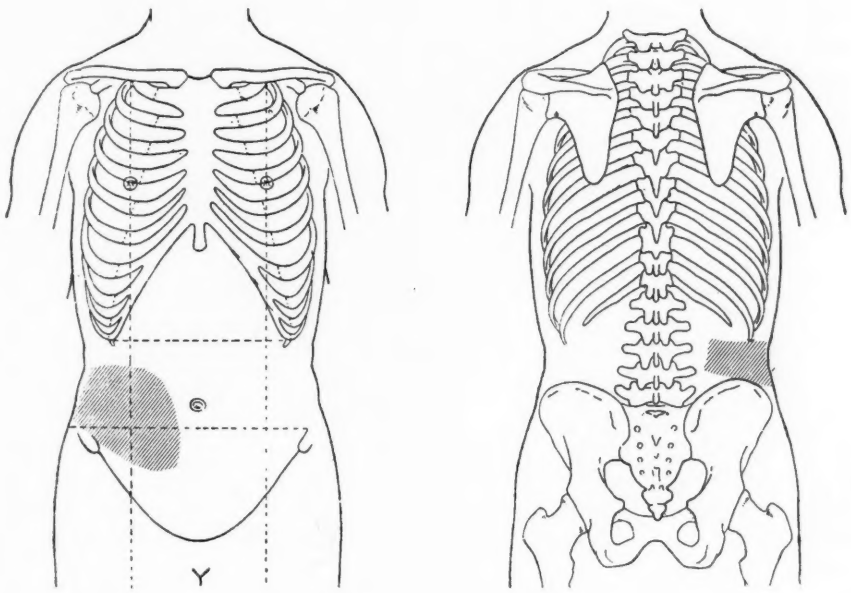


CHART 8 A.

Kelly and Hurdon also regard cutaneous hyperaesthesia as proof of peritonitis.

On the other hand Sir W. H. Allchin does not mention cutaneous tenderness in his contribution (*b*) on Acute Peritonitis to Allbutt and Rolleston's *System of Medicine*, nor in his article (*a*) on Perityphlitis in his own *Manual*. Dr. Head is emphatic on the subject, though I think mistaken :—

'There is no true cutaneous tenderness in peritonitis, and the tenderness that is present differs fundamentally in character from that which accompanies referred pain. If the skin only is picked up between the finger and thumb in a case of acute peritonitis, the patient complains of no pain. . . .'

Another of my cases is a good instance in point of this disputed question. The patient was a boy of 15, admitted on the eighth day of his first attack of appendicitis with signs and symptoms of widespread peritonitis. It was held to be a hopeless case, and the boy died unoperated on; the diagnosis was confirmed by post-mortem examination, at which the appendix was found to contain a stercolith and to be both gangrenous and perforated. On admission he presented a large area of cutaneous tenderness, as shown on Chart 8A, and five hours later it had so increased as to occupy the whole surface of the abdomen and loins, with the exception of small spaces in the epigastrium and above the pubes. The tender area crossed Poupart's ligament into the thigh on both sides (Chart 8B), but it will be noticed that it kept strictly within the territory

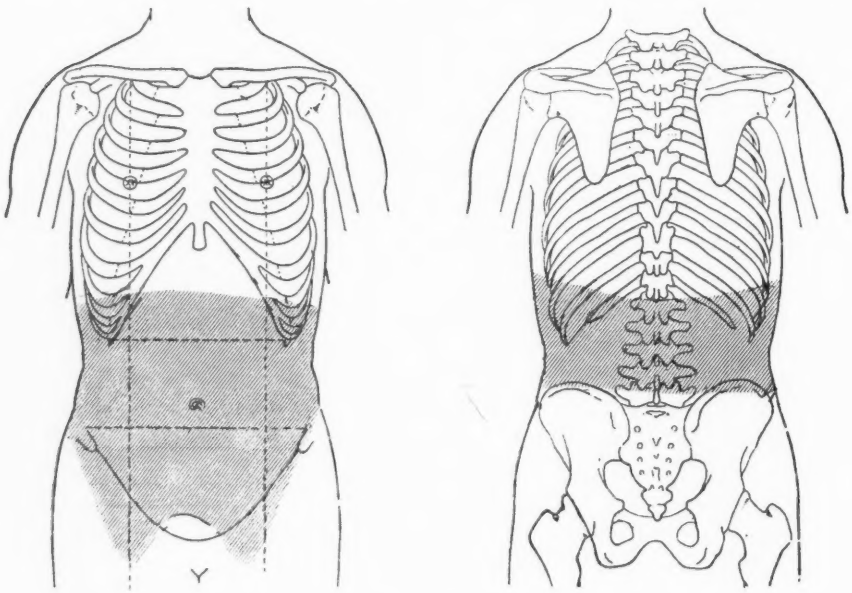


CHART 8B.

of the twelfth dorsal segment, not at any point encroaching upon that of the first lumbar. There is no doubt that the original lesion was in the appendix, and, notwithstanding the manner in which cutaneous tenderness is known to spread beyond the limits of the areas originally attacked without corresponding increment of the provoking irritation, it is hard to suppose that such an extension could occur as rapidly and as widely as in this case. I feel driven to conclude that the peritonitis caused the cutaneous tenderness.

Another case of very widespread, if not actually general, peritonitis is recorded in my notes. Here a large area of cutaneous tenderness on the right side of the abdomen passed backwards as a narrow band into the loin (Chart 9). The patient died five days after operation, which was undertaken on the second

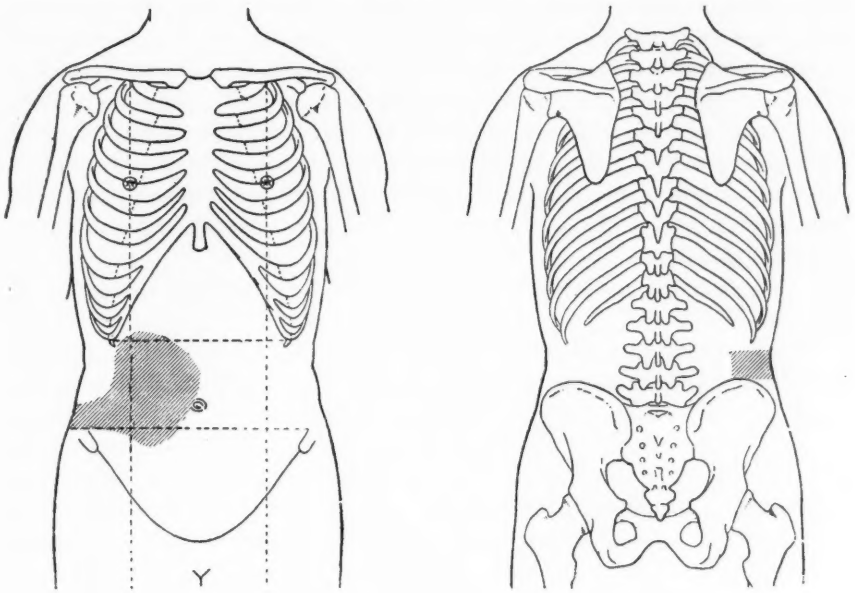


CHART 9.

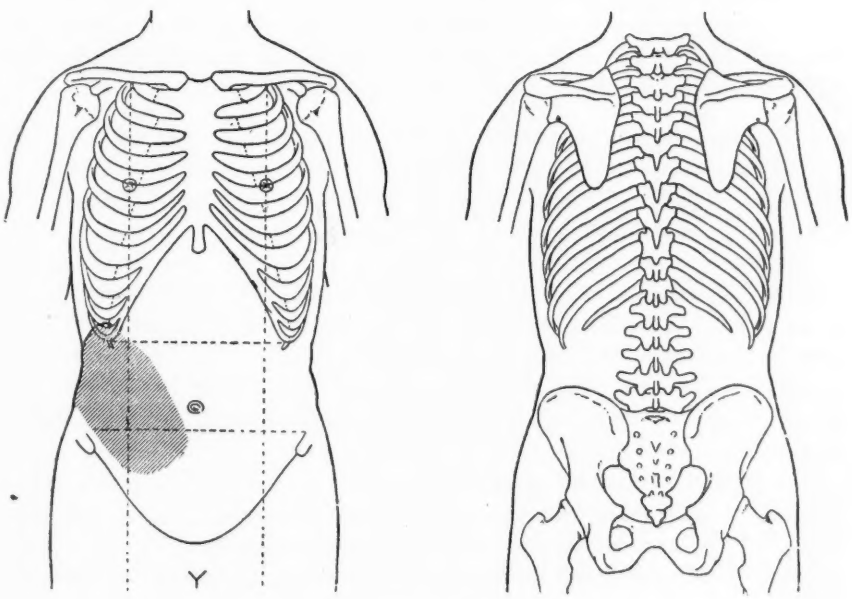


CHART 10.

day of his first attack of appendicitis; the appendix in this case was perforated and gangrenous.

Yet a fourth case of a large abscess, with marked absence of limiting adhesions, and a perforated sloughing gangrenous appendix, displayed a large irregular area of superficial tenderness (Chart 10): this patient recovered after drainage. A case in which when pinched there was tenderness all over, but when tested with a pin only in a limited region, may also have been one of general peritonitis. The case is noted as one of a large abscess, but the patient died three days later.

As against these, I find in my negative cases five of general peritonitis; all of them ended fatally.

Without adopting the view as to the necessarily peritoneal origin and serious import of cutaneous tenderness, it is at any rate established that this symptom may be found over large tracts of the abdomen in cases of extensive or general peritonitis. Moreover, it seems at all events probable that it is directly evoked by the inflammation of the peritoneum in those cases. The alternative assumption is, that in the grave toxaemia of extensive septic peritonitis the nervous system is affected in such a way as to evince reflex disturbances of wider distribution than in milder forms of appendicitis.

It is often taught, on the authority of Professor Lennander according to Dr. Hale White (*b*), that the peritoneal coat of the viscera is insensitive to tactile and painful stimuli, both in health and when inflamed; but that the parietal peritoneum is extremely sensitive. If that is so, a possible explanation of the conflicting views of the physicians and surgeons whom I have quoted may be this: that it is only when peritonitis becomes so generalized as to affect the parietal layer that it can evoke reflex cutaneous symptoms.

Many of the most instructive cases have already been mentioned in connexion with the points which they illustrate. There are, however, one or two which are worthy of recital in rather greater detail before I turn to the consideration of abdominal diseases other than appendicitis.

A woman, aged 52, applied for admission on the third day of her second attack of appendicitis. Clinically, her symptoms suggested a fulminating lesion of the most acute nature. Her pulse-rate was 156, her temperature 101° F., not only when registered in the receiving room, but afterwards also in the ward to which she was sent. The abdomen was rigid, and almost motionless, with a tender mass in the right iliac fossa. She had a perfectly definite patch of superficial tenderness.

Here, then, was a case apparently in urgent need of instant operation, but with definite cutaneous tenderness. It seemed likely, from the signs and symptoms of the patient, that gangrene, perforation, abscess, general peritonitis, any or all of them, would be disclosed by laparotomy. In this case, however, the interpretation which Mr. Sherren would have assigned to the presence of cutaneous tenderness turned out to be correct: the vermiform appendix, when removed,

was apparently normal externally, though when cut open it was found injected and catarrhal. The patient made a rapid and satisfactory recovery, and a further point of interest is that she was subsequently readmitted for biliary colic, and displayed then no superficial tenderness.

An unusually low site was affected by cutaneous tenderness in one case; this was in a woman of 21, seen on the second day of an acute first attack, which was coincident with the onset of menstruation (Chart 11). In the appendix of this patient there could be no doubt about the existence of tension: for it was swollen, stiff and kinked; and when the kink was unfolded, much

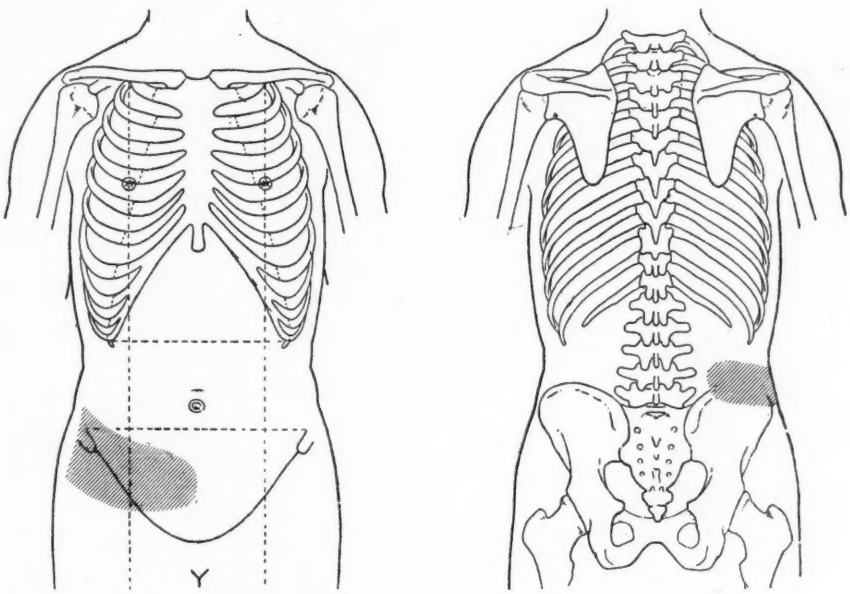


CHART 11.

fluid ran back from the distended distal end into the caecum. There were also found numerous small haemorrhages in the mucous membrane.

A very extensive area of tenderness is delineated in Chart 12, that of a female patient, 25 years of age, seen on the fourth day of her first attack. The symptoms and signs were those of an acute lesion, and the appendix was removed at once, but was apparently healthy except for a little stiffness near the tip. Microscopically there was found a condition of catarrhal appendicitis. Two days after the operation the patient developed lobar pneumonia on the right side, but it is difficult to prove that there was any connexion between this and the cutaneous tenderness.[4] Convalescence was satisfactory.

[4] Mr. H. W. Carson says: 'If there is extreme cutaneous hyperaesthesia' (in appendicitis) 'suspect chest trouble, especially in children' (*Brit. Med. Journ.*, 1906, ii).

Before passing on to the statistics of other abdominal crises, it is worth comparing the incidence of cutaneous tenderness in men and in women. Most English authors assign a preponderance of cases of appendicitis to the male sex, and Sir W. H. Allchin puts the percentage as high as 80. Professor Osler, on the contrary, thinks the proportions are about equal. Of the 123 patients dealt with here, there were 77 males and 46 females; that is, 62·6 % and 37·4 % respectively. Now of the positive cases there were but 12 males as against 14 females; it appears, therefore, that the nervous system reacts to stimulation from the appendix more readily in women, as might be expected, than in men.

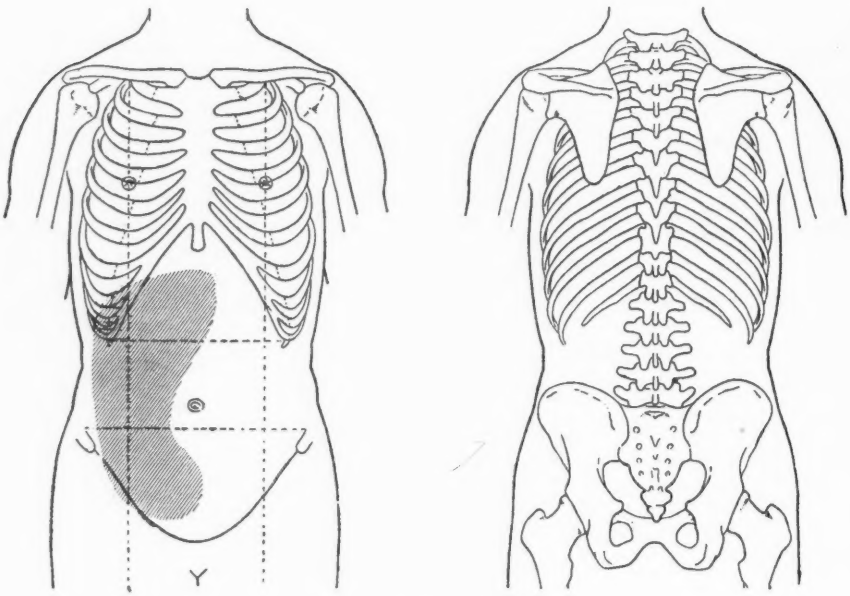


CHART 12.

I now turn to the notes of 71 patients who were observed while suffering from acute abdominal disorders not being appendicitis. Here also I shall quote Mr. Sherren's words:—

'The cutaneous hyperalgesia met with in renal colic might be mistaken for that of appendicitis, but as a rule is higher, more widespread, and tends to pass down into the first lumbar area; where an anterior area only is left, it is over the margin of the bony thorax about the situation of the 10th and 11th ribs."

It is to be noted in passing that Mr. Sherren is not in agreement with Drs. Mackenzie and Head on this point. For the former of these physicians describes a case of renal colic, verified by operation, associated with tenderness of the skin in the right iliac fossa (*b*); and the latter's remarks are somewhat in the same sense (*a*). I have myself looked for superficial tenderness in only two

cases of renal colic, and found it in neither. There is one interesting case in my records, however, which possibly bears upon the matter, so I recite it now. A girl of 18 suffered some internal injury by falling off the twelfth step of a step-ladder, and was shortly afterwards admitted to hospital with signs of intra-peritoneal haemorrhage. For twenty-four hours she exhibited cutaneous tenderness as in Chart 13. At the end of that time this symptom disappeared, but the quantity of intra-peritoneal fluid increased slowly for two days more, after which it began to diminish and finally disappeared. There was, so far as could be ascertained, no fracture of the pelvis; nor was there any haematuria; nor

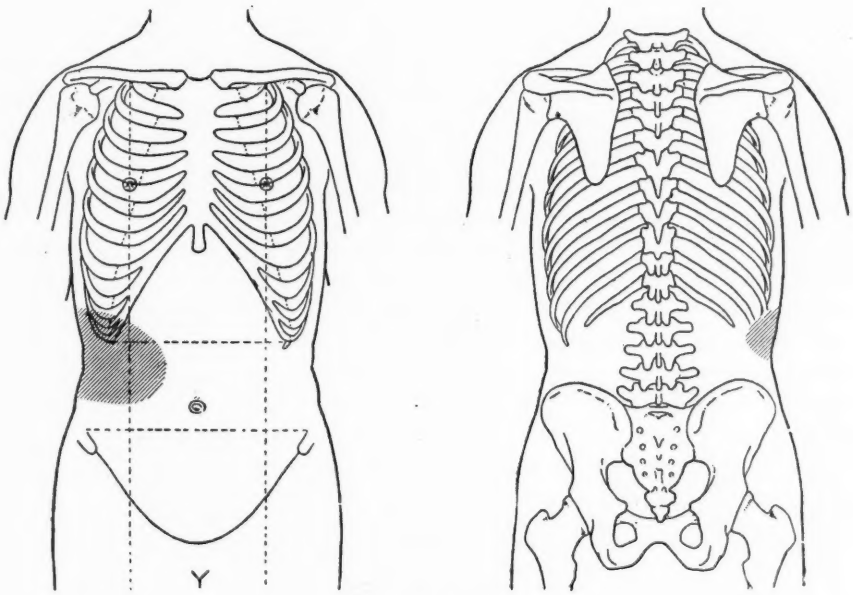


CHART 13.

a history suggestive of an ectopic gestation; and the source of the haemorrhage remained a mystery. A partial rupture of the kidney, which is not always followed by haematuria, seemed the most likely explanation of the case; if this had occurred, the cutaneous tenderness may have been excited by a clot of blood in the renal pelvis.

Mr. Sherren continues:—

'The areas met with occasionally in gall-stones and gastric ulcer are too high to be mistaken for those of appendicitis, and in gastric ulcer the symptom is often present only on the left side. Inflammation of the uterine appendages may give rise to cutaneous hyperalgesia, but its occurrence is rare, and it is as a rule bilateral.'

In gall-stone cases I have found three positive out of seven. The areas are undoubtedly higher than in ordinary appendix cases, but they seem to vary

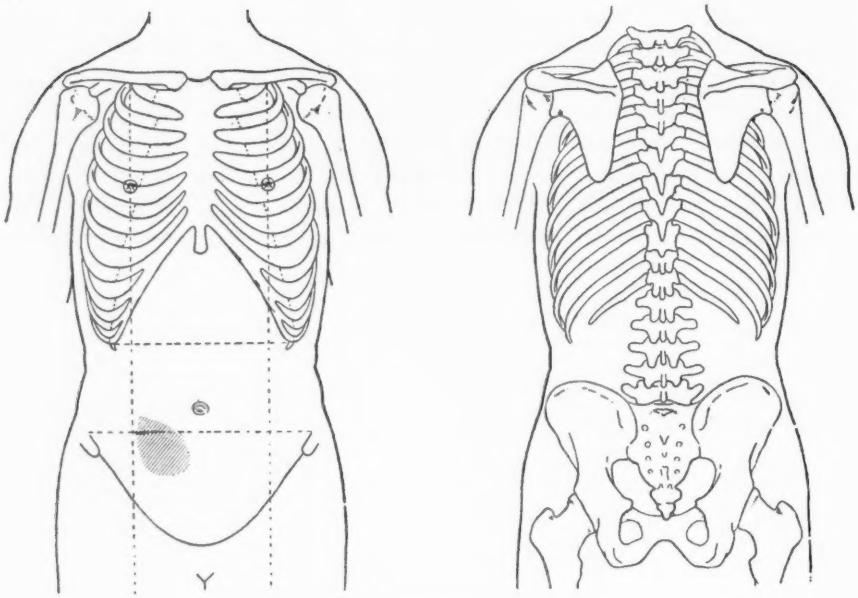


CHART 14 A.

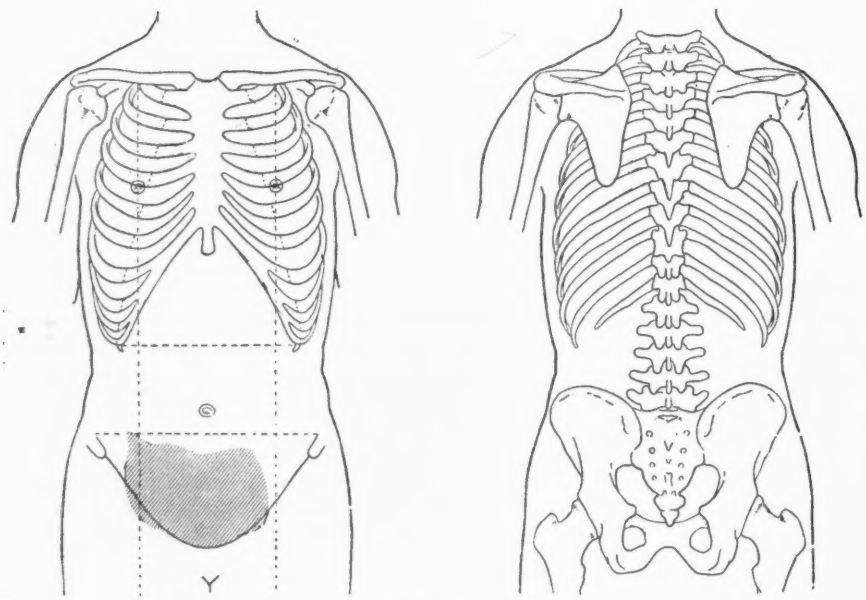


CHART 14 B.

somewhat in position, and a low gall-stone patch might perhaps be confused with one due to appendicitis. One of the four negative cases, as I have already mentioned, had previously been a positive instance of this latter disease.

The first of these patients possessed a small elliptical area just above and internal to the anterior superior iliac spine; his gall-bladder contained some hundreds of small stones. The second had a small circular patch close to the costal margin, and the third a larger area passing back into the loin. I saw no instance of the double bands which Dr. Head has described in gall-stone cases, and Mr. Sherren tells me that he, also, has not met with them.

In simple gastric ulcer tenderness of the skin is frequent, and has been noted by many writers, but it is, as Mr. Sherren says, left-sided or median as a rule; and also, I think, more indefinite in its boundaries and more frequently associated with spots of maximum intensity than are the other conditions which I have studied. The late Dr. Julius Dreschfeld thought otherwise, for when discussing hyperaesthesia of the skin in gastric ulcer, he states that it is generally sharply defined. Dr. Head, I think, is of the opposite opinion, which I have just expressed.

In six cases of perimetritis there were two with cutaneous tenderness. In one of these there was a small patch quite similar to that seen in many cases of appendicitis: in the other was found at first a typical 'appendix triangle' which afterwards spread over to the left side (Charts 14 A and 14 B). Cases of disease of the uterine appendages which gain admittance to general surgical wards are nearly always right-sided in nature; for otherwise they do not cause suspicion of appendicitis, and are dealt with by a gynaecologist. It is, therefore, not to be concluded from these statistics that perimetritis is commonly attended by cutaneous symptoms liable to be mistaken for those of appendicitis.

A detailed statement of the 71 cases is appended:—

a. Gastric and duodenal ulcer: { simple, 7 cases. / perforated, 7 cases.

Of the simple cases, five had cutaneous tenderness, but none of these in the least resembled appendicitis in this respect. Of the perforated cases six were negative; but the other, a perforated duodenal ulcer, exhibited a band indistinguishable from those caused by appendicitis (Chart 15). There was extensive peritonitis, and the outer surface of the appendix shared in this inflammation. The symptoms were those of severe appendicitis, and the operation was begun in accordance with that diagnosis.

b. Acute intestinal obstruction: 9 cases, all negative.

c. Strangulated hernia: 7 cases; one of these, a left-sided case, had a large area of cutaneous tenderness in the territory of the 12th dorsal and 1st lumbar nerves (Chart 16). Dr. Head described two cases of strangulated hernia with cutaneous tenderness of the 10th dorsal area. In view of the great length and

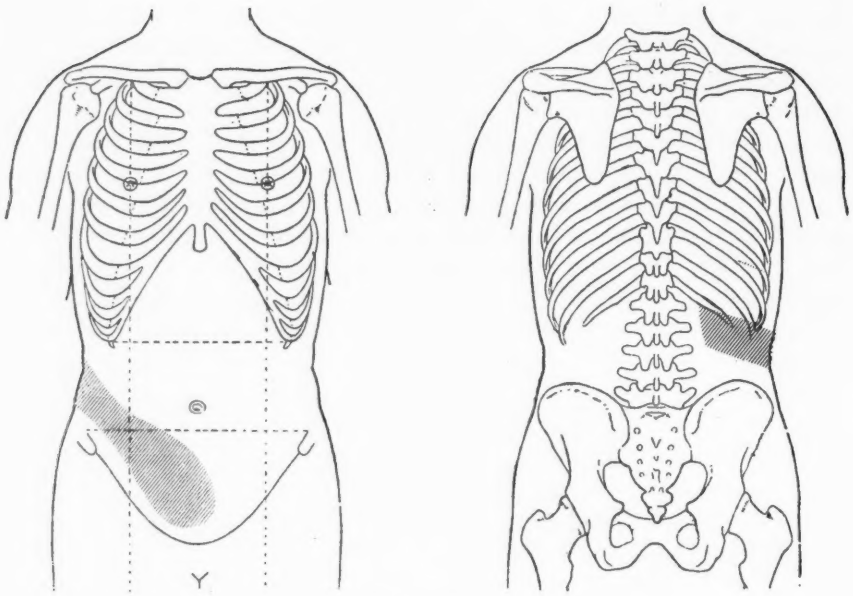


CHART 15.

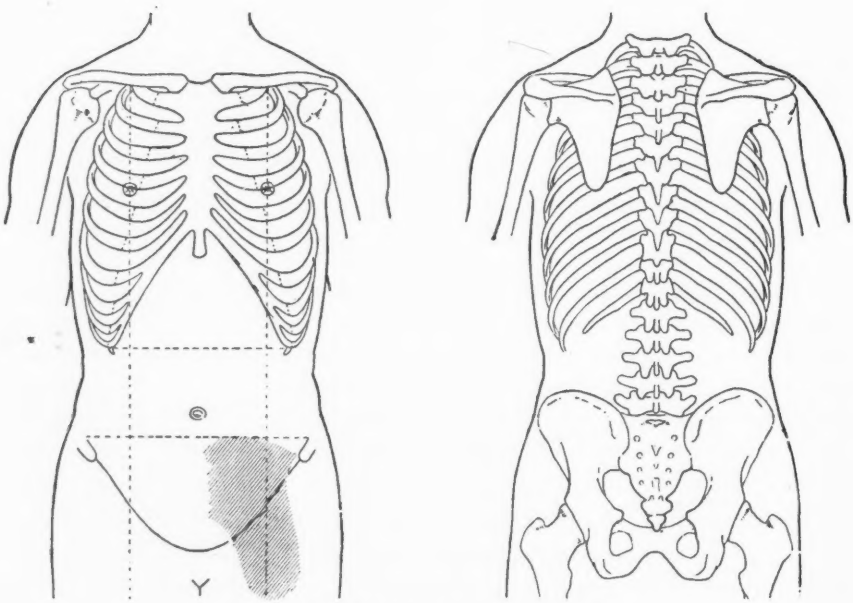


CHART 16. (Upper margins very indefinite.)

extensive nerve supply of the gut, it is not surprising that different examples of the lesion under consideration should produce varying segmental disturbance.

d. Obstructed hernia: 5 cases, all negative.

e. Gall-stones and cholecystitis: 7 cases. Three of these were positive, as already described.

f. Perimetritis: 6 cases, two positive.

g. Pyosalpinx and salpingitis: 4 cases, all negative.

h. Renal colic: 2 cases, both negative.

j. Ruptured ectopic gestation: 1 case, negative.

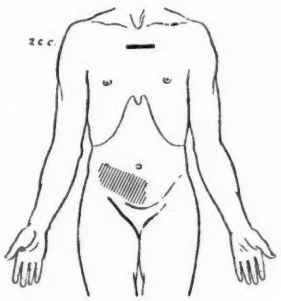


CHART 17 A.

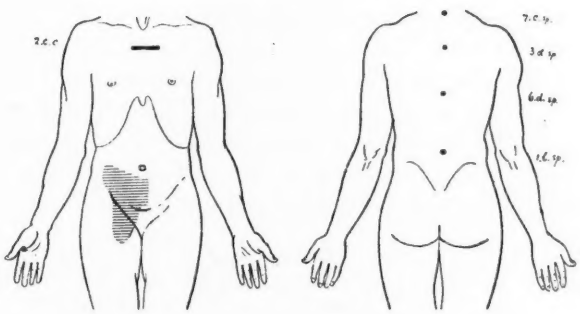


CHART 17 B.

k. Movable kidney (Dietl's crisis): 1 case, negative.

l. Carcinoma of the stomach: " "

m. Neuromimesis of perforated gastric ulcer: " "

n. Tuberculous peritonitis: " "

o. Pancreatitis: " "

p. 'Surgical kidney': " "

q. Colic from a surfeit of currants: 1 case. The symptoms were apparently those of appendicitis, and a patch of superficial tenderness was also found (Chart 17 A). When tested again just before operation, about twelve hours after admission, this area was found invading the thigh (Chart 17 B). The appendix

looked healthy, and was so reported when microscopically examined. Just before operation an enema resulted in the recovery of a 'jugful' of currants, and a similar quantity was obtained by another enema on the following day. The migration of the tender area in this case is very interesting; for it is a plausible suggestion that the offending currants had passed along the intestines during the interval, and so irritated a portion of gut supplied from a lower segment of the spinal cord.

r. Peritoneal haemorrhage after injury: 1 case, described above.

s. Doubtful: 8 cases. Two of these displayed cutaneous tenderness, but, as the diagnosis was never established, there is little to be gained by considering them.

Of the 16 positive cases among the 71 which have just been classified, there were five which might possibly be confused with the commoner appendicitis areas, and certainly in most of these the diagnosis was not at first clearly established; or rather, appendicitis was not evidently out of court. During the same time there entered the hospital 26 positive cases of appendicitis. It is a legitimate deduction that, of patients affected with acute abdominal disease and displaying superficial tenderness in the 11th dorsal area of control, a fair percentage are not cases of appendicitis at all, though the majority are.

Theoretically, too, it seems to me that, since the 11th dorsal segment does not supply the appendix alone among the abdominal viscera, there is no anatomical reason why lesions of other organs should not result in superficial tenderness in the territory of the cutaneous nerve-fibres of that segment, and of shapes similar to those which may result from stimulation by the appendix. On the other hand, it may be said that such bands and triangles (of cutaneous tenderness) are not found on the left side; and this, if universally true, would require explanation. However, though I have not myself seen such left-sided areas, Dr. Head figures (*a*) instances thereof in various conditions.

Summary of Deductions and Conclusions

I shall now embody my deductions in a series of propositions, of which some are a repetition of Mr. Sherren's conclusions, and others are not: and to avoid confusion they will be numbered in Arabic numerals instead of Roman.

1. In diseases of the vermiform appendix, or originating there, cutaneous tenderness is sometimes present: most commonly in the skin innervated from the 11th dorsal segment of the spinal cord, but also sometimes in the territory of the 9th, 10th, and 12th dorsal, and possibly of the 8th dorsal and 1st lumbar segments.

2. The areas of such tenderness are most frequently of three main forms described by Mr. Sherren in the *Lancet* of September 19, 1903. But cases are not rare in which the areas are irregular and atypical altogether.

3. A patient displaying an area of superficial tenderness of one of these

three defined varieties is in the great majority of cases suffering from appendicitis.

4. Nevertheless many other diseases may resemble appendicitis in this respect: for instance, renal colic, perforated duodenal ulcer, intestinal colic, perimetritis.

5. Inflammation of the nerve trunks is not the cause of this symptom, for the latter may occur in skin supplied by the posterior primary divisions of the spinal nerves.

6. There is little evidence as to the immediate cause of this reflex tenderness, but it is probably irritation of the afferent nerves from the appendix: the irritant is possibly in some cases tension, in others it is almost certainly something different.

7. The symptom is found in a minority only of the cases of appendicitis seen in hospital practice. It may vary in character, or disappear altogether, while a case is under observation: during the progress of an attack it may appear in a patient in whom it has not originally been present.

8. Cutaneous tenderness is found as frequently in subsequent as in first attacks of appendicitis. It may persist long after all other signs of the disease have disappeared.

9. The prognostic and therapeutic significance of cutaneous tenderness in cases of appendicitis is slight. It is somewhat less often found in cases of abscess than in other cases: when the symptom and an abscess coexist, it is usually in an early case.

10. Cases of widespread peritonitis set up by appendicitis may display large areas of cutaneous tenderness over the right side or over the whole, of the abdomen.

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ON THE ORIGIN OF ENDOGENOUS URIC ACID

By E. P. CATHCART, E. L. KENNAWAY and J. B. LEATHES

In a recent paper by Hirschstein, the fact that the rate at which uric acid is discharged from the body is greater during the day than it is at night is explained as being due to the retention of uric acid during sleep, and the fact that it is during the first waking hours that this rate is greater than at any other time in the day is ascribed to the rapid discharge of the uric acid that has accumulated during the night. This theory, which seems to imply that the rate at which the uric acid is produced in the body is fairly constant at all times of the day, is supported by the following experimental evidence :—

After a day on which food free from purin derivatives was given, a patient was put on a regular diet of three meals at 7 a.m., noon, and 6 p.m., each of which had the same composition, bread, milk, butter, an egg and an apple. On the third day, in addition to the usual breakfast, 250 g. of calf's thymus was given, on the fifth day the same addition was made to the midday meal, and on the seventh day to the evening meal. The considerable increase in the output of uric acid, that is known to follow such an amount of thymus as this, might be expected, if there is a tendency for uric acid to be retained at night, to appear in the urine later when the thymus was given in the evening, than when it was given in the morning. The urine was collected and examined every eight hours, but the results may be given as follows :—

Table I.

	Mg. uric acid excreted 24 hours	48 hours	Average in 24 hours
1st day	284	585	292
2nd day	301		
3rd day +250 g. thymus at 7 a.m.	385	612	306
4th day	227		
5th day +250 g. thymus at 12 noon	301	469	234
6th day	168		
7th day +250 g. thymus at 6 p.m.	261	385	269
8th day	124		
9th day	423		

In the last column but one of this table the output of uric acid in successive periods of 48 hours each is given, in the first of which periods no thymus was given, in the next three, at some time in the course of the first 12 hours out of the 48, 250 g. of thymus was added to the ordinary food. If the output

on the first two days is taken as a standard for comparison, as is presumably intended, then we have to note the remarkable fact, that the addition of the thymus caused an increased output of uric acid amounting to 30 mg. on the first occasion on which it was given, but after that the subsequent additions of thymus resulted actually in a smaller, and in fact considerably smaller, output than on the days when the food contained no purin compounds. Now Burian and Schur reckon that 100 g. of calf's thymus contains 0·45 g. of nitrogen in the form of purin bases; 250 g. therefore contain 1·125 g. Of this they find about one quarter or 0·28 g. appears in the urine, which, if it were all in the form of uric acid, would amount to 0·84 g., or allowing for some less completely oxidized purin base, to anything from 0·5 to 0·75 g. of uric acid. The figures given by Hirschstein are of quite a different character, and so far from justifying inferences as to the normal course of the excretion of endogenous uric acid, seem rather to call for some explanation of their abnormality. Whether that might be found in the fact that the subject selected for the experiment was convalescent from pneumonia and not yet out of bed, it is not possible to say. But during and after the crisis of pneumonia a great loss of nuclear material is known to occur, and it is possible that this loss may during convalescence be followed by retention of purin compounds in the food.

Before the appearance of Hirschstein's paper, one of us had tried to meet the possibility of the low output of uric acid at night being ascribed to retention, in some experiments to be described later. But the indications given by these experiments seemed to point to a conclusion different from that for which Hirschstein argued. And it therefore seemed necessary to repeat the experiment with the thymus under conditions which might be expected to lead to a less confusing result.

From September 1 to September 29 (vide protocols at end of this paper, Table IX) four meals were taken daily at 8.30 a.m., 12.30, 4.30 and 8.30 p.m., each consisting as in earlier experiments of a pint (570 c.c.) of milk, 6 ozs. (170 g.) of bread and 1 oz. (28 g.) of butter, and three preserved plums. The urine was collected at these hours immediately before the meals, and again at 11.30 p.m.: the five samples being analysed separately. The average rate at which uric acid was excreted at each of these periods of the day was calculated from the actual observations extending over nearly four weeks, not counting those periods in which the effect of the thymus taken could be detected. Calf's thymus, 173 g., was taken on two occasions, at 8.30 a.m. on the 13th and at 8.30 p.m. on the 14th, it being substituted for the amount of bread calculated to have a corresponding food value.

In the following table the effect on the output of uric acid is shown, the figures given being the amount excreted over and above the average amounts for the corresponding times of the day:—

TABLE II.

Amount of additional uric acid excreted over and above the normal average was	After taking 173 g. thymus at 8.30 a.m.	After taking 173 g. thymus at 8.30 p.m.
In the first 12 hours	204	221
In the first 24 hours	410	444
In the first 28 hours	428	476

After 28 hours in each case the observed rates were normal.

The curves in Fig. 1 show the rate at which this additional uric acid was excreted in each of the four-hour periods—the dotted line, that after the thymus had been taken in the morning; the unbroken line after it had been taken in the evening. The horizontal abscissa marked out into periods of four hours each, represents in each of these periods the average normal rate of excretion of uric acid for that period.

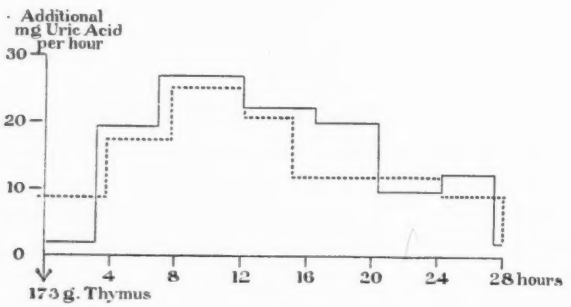

FIG. 1.

This figure shows clearly that there was not the slightest indication of retention of uric acid at night, when the thymus was given in the evening. The amount of uric acid excreted over and above the average amount after each meal of thymus agrees fairly well with the estimations of Burian and Schur. In 173 g. of thymus, containing 0·45% of nitrogen in the form of purin bases, there would be 0·778 g. of such nitrogen. Of this, one quarter should appear in the urine, or 0·195 g. if the total purin compounds excreted were determined. The uric acid alone was estimated, and in 0·428 and 0·476 g. of uric acid there is 0·143 and 0·159 g. of nitrogen respectively. Had the total purin bases been determined, these figures would have risen to values very close to the normal estimates of Burian and Schur.

This result therefore is confirmed by its consistency with previous experience, and if it is fair to argue from the fate of exogenous to that of endogenous uric acid, which is the premiss on which Hirschstein's argument is based and probably correctly based, then the inference is that the output of uric acid is

normally low at night and high in the morning, not because as much uric acid is formed during the night as during the day and some of it retained till the morning, but because the rate of production is lower during the night than the day, and higher in the first hours of the day than during the later hours. From this too it follows, as was argued in an earlier paper (Leathes), that the diurnal fluctuations in the rate of uric acid excretion correspond to fluctuations in the activity of some function or functions of which the endogenous uric acid is the chemical expression.

It is possible to induce diuresis and an increase in the rate of excretion of nitrogen, to overcome, as it might be put, a tendency to the retention of nitrogen at night, by drinking water at intervals during the night. This was done on Feb. 23, 1907 (Table VI), when at 1 a.m. and again at 5 a.m. 200 c.c. of water were taken. The nitrogen output and also that of creatinin was above the average in both the next samples of urine, collected at 8.30 a.m. and 2 p.m., but the output of uric acid was, notwithstanding, below the average in both periods. An attempt was also made to test this point, on the lines of the better experiment devised by Hirschstein and published some months later, by taking urate of sodium in the evening on Feb. 26, and in the morning of Feb. 28. But the fact that uric acid is very slightly absorbed from the intestine had been overlooked, and no definite result was attained.

Hirschstein however; having stated that the daily fluctuation in the output of endogenous uric acid is undoubtedly due to nocturnal retention, and that his experiment proves it, nevertheless in another part of his paper raises the question whether it may not be due to other causes, muscular activity on the one hand or activity of the digestive organs on the other. That muscular activity does not influence the output he considers is proved by an experiment in which a patient taking the same purin-free food on four successive days, excreted on the first two days when he was kept in bed, 0·381 and 0·359 g. of uric acid, and then on the next two days, when he was up, excreted 0·300 and 0·332 g. But as a result of his experiments on the relation of activity of the digestive organs to endogenous uric acid he concludes that at least 70% of the output is to be attributed to this form of activity, a conclusion which there must be difficulty in reconciling with his conclusion as to the significance of nocturnal retention which we have been discussing.

In an earlier paper (Cathcart and Leathes) an experiment was described in which it was shown that during severe muscular exertions the output of uric acid was diminished, but that later, after the activity had ceased, an increase in the rate of output occurred which lasted for one or two days. An epitome of the evidence which we have collected on these points is here given, and shows, since most of it was obtained from other subjects and under varying conditions, that they may be generally applied.

1. Aug. 20, 1906. (J. B. L.) 8th day of bread, butter, and milk diet, taken in identical meals every 3 hours from 7 a.m. till 10 p.m. The urine was examined every 3 hours. Between 1 and 4 p.m. the subject bicycled for 2½ hours

on a hilly road, about 30 miles in hot weather. The rate of uric acid excretion during the 3 hours was 13 mg. per hour, as compared with the average rate for that time of day, 30·7 mg. per hour, and the rate during the preceding 3 hours 35·9 mg. per hour. During the following 24 hours the total output was 0·640 g. and during the next 24 hours after that 0·568 g. The total nitrogen excretion during the ride was at the rate of 0·83 g. per hour, and the average rate for this time of day 0·81 g. per hour.

2. May 28 and 31, 1907. (E.P.C., vide protocols, Table VIII.) On the first of these occasions muscular exertions were carried out stripped, and heat loss was accelerated by cold sponging. In the hours during which the muscular work was done, the rate of uric acid excretion fell from the average rate for that period of the day of 13 mg. to 6·2 mg. per hour: nevertheless, in the 24 hours beginning with the exercise the total output amounted to 0·396 g. as compared with the average of 0·321 g. As is pointed out in the paper where the experiment is fully described, this increased output is in part due to the effect of cold. Three days later severe exertions were again undertaken, only this time in heavy clothing. The output for the period during which the muscular activity occurred was at the very low rate of 3·6 mg. per hour as compared with the average rate of 13 mg. For some time after the rates were low, so that in the 24 hours beginning from the period of activity only 0·223 g. was excreted: in the two succeeding periods of 24 hours, however, the output was above the average—0·375 and 0·354 g. respectively—the average output for 24 hours being 0·325 g.

3. Sept. 10, 1907. (J. B. L., v. Table IX.) In the course of 3 hours two 10 lb. dumb-bells were lifted 720 times from the ground to above the head, and other active movements, running and jumping, were carried out in the intervals. The rectal temperature, which was 99·0° at the beginning, rose to 101·2° and was over 100° during the greater part of the time. The uric acid output during the 4-hour period in which the exercise was taken fell from the average rate for this period of 30·4 to 19·9 mg. per hour, but rose in the next period to 44·6 (average 30·6) and was maintained above the average for 48 hours. In the first 24 hours after the exertion the output was 0·866 g., in the second, 0·715: the average for 24 hours for the whole experiment (22 days) was 0·652. In this case the total nitrogen excretion was 26 % below the average during the exercise, and during the first 24 hours the output of nitrogen was 2·7 g. below the average (15·6 g. instead of 18·3). The subjective effect was a great amount of general stiffness and soreness, especially in the back and shoulders.

4. Sept. 19, 1907. (J. B. L., v. Table IX.) At the same time of the day and for the same length of time, similar movements were carried out, only the weight of each dumb-bell was 3 lbs. instead of 10. The exertions involved therefore considerably less work, and were also carried out with considerably greater ease, owing to the practice acquired in the previous experiment. They were accordingly followed by far less fatigue and stiffness. The output of uric acid in the period including the exercise was at the rate of 23·5 mg. as

compared with the average for this period of 30·4, and with the figure on Sept. 10 of 19·9 mg. per hour. But in the succeeding 24 hours the output was just about the normal average 0·644 g. (average 0·652). The total nitrogen excretion was hardly affected at all. The temperature during the work did not rise to 100° at any time.

5. Sept. 28, 1907. (J. B. L., v. Table IX.) During the whole of this month the meals of bread, butter and milk were taken at 8.30 a.m., 12.30, 4.30 and 8.30 p.m. On this day the first meal was omitted, but one pint of water was taken instead of the usual pint of milk. The exercise, bicycling, began at 10, and at 12.30, when 23 miles had been covered, the first meal was taken. About 50 miles were completed by 4.30. The riding was against a strong wind, and there were delays due to the meal at 12.30 and later to accidents. The output of uric acid from 8.30 to 12.30 was at the rate of 29·3 mg. per hour (the average rate for these hours = 31·9), from 12·30 to 4.30 34·8 mg. per hour (average rate 30·4), while in the period from 4.30 to 8·30 after the ride was over, it rose to 47 mg. per hour when the normal average rate was 30·6. In the 24 hours ending at 12.30 p.m. on the 29th 0·806 g. of uric acid was excreted, the average for 24 hours in this month being 0·652 g. The nitrogen excretion was low during the ride, partly due to the fact that the first meal of the day had been omitted, but in the 24 hours ending at 12.30 on the 29th, the total output was about 2 g. above the average.

6. Nov. 7, 1907. (E. L. K., v. Table X.) This and the next two experiments were part of a long series, for which the subject took daily, from October 30 to December 1, three identical meals of bread and milk at 9 a.m., 2 and 7 p.m. The urine was collected at these hours, and also at 12 at night. On November 7, four hours' moderate exercise was taken, walking, from 10 a.m. to 2 p.m. The rate of uric acid excretion was during this period slightly higher than it had been at this period of the day. But during the night and on the following day it was noticeably increased, 0·483 g. being excreted, as compared with the average from 21 normal days, of 0·429.

7. Nov. 9, 1907. (E. L. K., v. Table X.) Severe muscular work, sawing and chopping wood, was done from 10 a.m. to 3 p.m. The uric acid output from 9 a.m. to 2 p.m. was at the rate of 19·3 mg. per hour, being somewhat below the average rate on normal days, which was 23·3 mg. per hour. From 2 p.m. to 7 p.m. it was at the rate of 50·2 mg. per hour, the normal rate being 20·7. In the 24 hours ending at 9 a.m. on the 10th 0·796 g., in the next 24 hours 0·648 g. and even in the third 24 hours 0·471 g. were excreted, the normal average amount for 24 hours being 0·429 g. In the three days, therefore, after the beginning of the work 0·628 g. more uric acid was excreted than was normal. The exertions were such as to cause intense stiffness and aching all over the body, lasting for several days.

8. Dec. 1, 1907. (E. L. K., v. Table X.) On this day the meal at 8.30 was omitted, but an amount of water was taken equal to the amount of milk that was usually taken. From 9 a.m. to 11 a.m. severe dumb-bell exercises were

performed, (10 lb. in each hand lifted 1,000 times from the ground to above the head). The urine excreted from 9 to 11 a.m. was analysed separately from that from 11 to 2 p.m. In the former, the uric acid corresponded to an output of 4·8 mg. per hour, in the latter to 32 mg. per hour, the average normal rate from 9 a.m. to 2 p.m. being 23·3 mg. per hour. From 2 to 7 p.m., when the experiment ended, the rate rose further to 48 mg. per hour, the normal being 20·7.

From the results of these experiments the two facts which stand out clearly are—

(1) That *during severe muscular exertions the output of uric acid is lowered*; the output of nitrogen in all forms is generally unaffected, and that of creatinin is also only slightly if at all altered (vide protocols at end of the paper). There were only two occasions on which the uric acid was not diminished. In Experiment 6 of the above list, when the exercise consisted merely of walking for 4 hours, the rate of excretion during the walk was slightly greater than it had been before at this time of day, and during the latter part of the bicycling in Experiment 5 it was a little above the average: but then, about $1\frac{1}{2}$ hours out of the 4 hours of this period were spent resting for food and for repairs to the bicycle.

(2) *Muscular activity is followed by the excretion of uric acid in greater amounts than are normal, and this increased excretion may last for* 48 *or* 72 *hours.* If the exertions are considerable, the net result of these two effects is a marked increase in the output of uric acid.

In a number of experiments mostly earlier than those included in the above list the effect of muscular activity was left somewhat ambiguous, and for some time no satisfactory account of the result of such a change in the conditions could be given. It was not till a certain number of irregular results had been obtained that it appeared that the other intercurrent factor to which the irregularities were due might be the external temperature. The results of this nature, which are included in the protocols at the end of this paper, were as follows:—

9. Nov. 20, 1906. (J. B. L., v. Table IV.) Bicycling for 2 hours about 20 miles in a very cold wind gave rise to a markedly high output of uric acid at the time—39 mg. per hour—as compared with the normal average of 33, and for the succeeding 12 hours, though the exertions had only been moderate, the output was uniformly above the normal.

10. Nov. 24, 1906. (J. B. L., v. Table IV.) Bicycling from 3 to 7 p.m., about 35 miles. On this occasion there was no wind, but the air was very damp and the evaporation of sweat and, consequently, heat loss was impeded, although the temperature of the air was not high. In this case the rate of excretion was below the average. The urine for this period included that excreted in the hours from 1 to 3 o'clock, when the rate was probably the same as in the preceding period—about 30 mg. per hour—so that the rate during the exercise was probably more below the average rate than appears to be the case—perhaps as much below the average as four days before during exercise it had been above it.

11. Jan. 27, 1907. (J. B. L., v. Table V.) Bicycling for 2 hours and skating 1 hour. Exertions moderate. The air temperature was just about 32° F., but the exercise, during the hour's skating at any rate, was accompanied with heat production out of proportion to the work done. The uric acid output was below the average rate.

12. Jan. 28, 1907. (J. B. L., v. Table V.) Moderate exercise and sweating indoors, giving an output of 30 % below the average for the time of day.

13. May 11, 1907. (J. B. L., v. Table VII.) Bicycling 30 miles in the course of 4 hours, warmly dressed on a warm day. The effect of this on the output of uric acid was obscured by intercurrent factors, so that the excretion appears to be at about the normal average rate.

Such results as these suggested that it was necessary to determine, if possible, more precisely the effect, if any, of variations in the external temperature and the rate of heat loss. That the external temperature had some influence on the output of uric acid was suggested also by the figures obtained on Nov. 20 to 23 (v. Table IV). The 21st and 22nd were exceptionally warm, mild days, and the output on these two days was lower than it had been at any time since the observations began on Nov. 6. On the 23rd the first definite attempt to test this influence of heat loss was made by dressing more lightly than the subject was accustomed to do even in the height of summer. The weather at the same time turned colder. In the first eight hours, from 9 a.m. to 5 p.m., 40 mg. more uric acid was produced than corresponded to the average rate, and 76 mg. more than in the same periods on the preceding warm day.

The most striking of the experiments especially planned to test this influence of external temperature on the output of uric acid were described in an earlier paper (Cathcart and Leathes). Without going over the ground covered by that paper the experiments showed that loss of heat might increase the output of uric acid more than 70 %. If, at the same time, muscular exertions occurred the effect was much less, while if severe muscular work were done in heavy clothing the output of uric acid during the period of the exertions almost disappeared, the figure 3·6 at 7 p.m. on May 30 being almost entirely accounted for by the correction, 2 drops of $\frac{N}{20}$ $KMnO_4$ only being used for the oxidation of the ammonium urate obtained from 80 c.c. of urine. The full protocol of this series of experiments (May, 1907) is included among those at the end of this paper (Table VIII).

A less-marked result, but still pointing in the same direction, was obtained on another subject on Sept. 6, 1907. The result is most obvious if the rates for this day are compared, not with the average for the whole month, but with those of the preceding day.

The counterpart of these results is contained in the results of staying in a room at the temperature of 37° C.

1. Jan. 29, 1907. (J. B. L., v. Table V.) The subject stayed in a hot room at 37° C. for 5 hours with, after an hour, an interval of half an hour for

the meal due at 1 o'clock. The output at both 1 o'clock and at 5 was 27 mg. per hour, the average rates being 32 and 31 mg. respectively.

2. Sept. 26, 1907. (J. B. L., v. Table XI.) The same experiment, but for 3 hours only. The output during this period, including these hours, was at the rate of 29 mg. per hour, whereas in the preceding and in the following period the rate was 36 mg. per hour.

The effect in both these experiments was not very pronounced, much less than during muscular work which is sufficiently active to raise the body temperature. But even in the first of these two experiments, when the stay in the hot room was longer than on the second occasion, the body temperature rose only 1° F.

It seems, therefore, possible to account for the different effects on the uric acid output that may be observed during the carrying out of muscular work as dependent upon the influence of heat loss or heat production. Rapid movement through cold air tends to increase the output, whereas the heat produced in muscular work tends to lower it, and the actual rate to be observed in any particular instance depends upon which of these two influences predominates.[1]

The later effect of muscular work, coming on after the work is over and lasting it may be for 48 hours or more, is the more remarkable of the two. It might be regarded as due to protracted excretion of the uric acid which was produced during the time when the muscles were active. But this is not the view that we take. We have failed to find any evidence for the idea that uric acid is apt to be retained in a normal individual.

Some of the arguments which led us to reject the idea that the normally low output at night is due to retention are capable of general application. But the most striking evidence on this point is furnished by the curve of uric acid excretion during a febrile rise of temperature which was published in an earlier paper (Leathes). That curve shows that as soon as the temperature begins to rise about 5 hours after a dose of typhoid vaccine the excretion of uric acid rises too, reaches its maximum when the temperature is at its maximum, and declines as the temperature declines. The maximum rate of excretion occurs at exactly the time when normally this rate is at its lowest, when, according to Hirschstein, uric acid is apt to be retained; and the decline occurs at the time when normally there is a rise, and, according to Hirschstein, the retained uric acid is flooded out. In this case, at any rate, it is clear that the rate of excretion of uric acid varies very closely with the rate of formation; it accompanies and runs parallel with

[1] On May 9, 1907 (v. Table VII) another and different effect of cold from the one described was obtained. On this occasion the measures adopted for effecting loss of body heat were far more energetic than in any of the other experiments we have done. The subject sat in a cold bath without moving and was continually sponged with fresh cold water for 70 minutes. The rectal temperature, which was 100·3 at the beginning of the treatment, had fallen 4° F. by the end of it. The output of uric acid was reduced 20% for 48 hours after this. The experiment has not been repeated because it was evident that the range of rates of heat loss within which physiological adaptation is possible had been considerably overstepped. Excessive stimulation seemed to result in depression.

the curve of body temperature, no less closely than the temperature curve corresponds to the tide of subjective sensations. There is not the slightest sign of retention or delayed excretion.

The amount of uric acid excreted over and above the normal average output in 48 hours, after severe muscular exertions of September 10, in the third of the experiments referred to above was 0·27 g., a very marked and considerable increase. But after a meal containing 173 g. of thymus in the experiment described in the first part of this paper, nearly twice as much, or nearly half a gramme of additional uric acid, was excreted in 28 hours, and at the end of that time the output was at the normal rate again. If, therefore, the 0·27 g. which resulted from muscular activity had been all produced during the work, the results of the thymus feeding experiments would lead one to expect it to be all excreted, at any rate, within 16 hours, or a third of the time over which its excretion was actually spread out.

It seems, therefore, probable that muscular activity intensifies the activity of certain processes which lead to the formation and excretion of uric acid, and causes this intensified activity to be maintained for a considerable time after the muscles have stopped working.

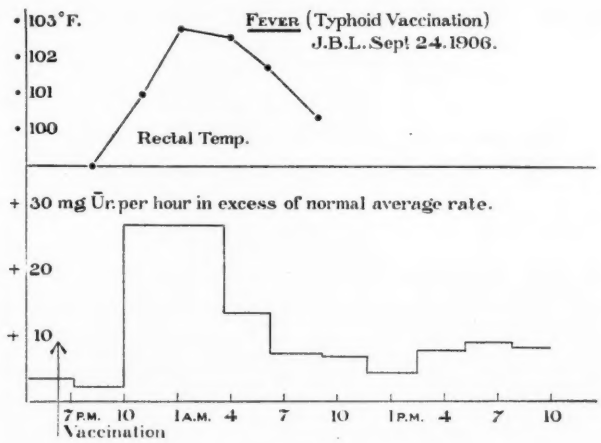

Fig. 2.

In the Figs. 2, 3, 4, and 5 the curves show the course of the acceleration in the rate of excretion of uric acid over and above the normal average rates. The zero line in these curves represents the normal average rate during each of the several periods of the day indicated by the numbers below this line. The ordinates of the curve give the excess of uric acid excreted during and after fever, exposure to cold, or muscular work as indicated in each figure. These curves serve to illustrate the points under discussion. They show that in fever (Fig. 2) the maximum rate is attained when the temperature is rising and at its

height, that as the temperature returns to normal the output of additional uric acid is diminished, though the normal rate is not re-established till more than 24

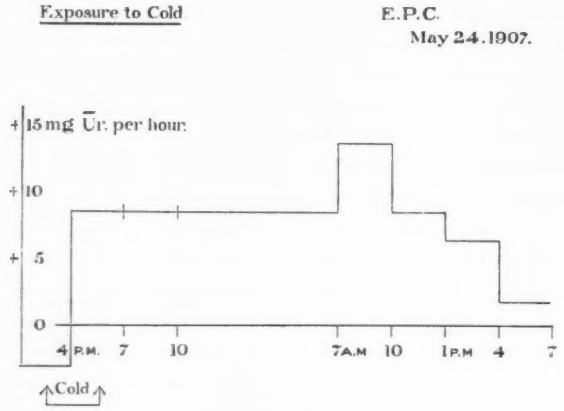

FIG. 3.

hours have passed: that muscular work (Figs. 4 and 5) causes an increased output which begins only after the work has stopped, at any rate if the work

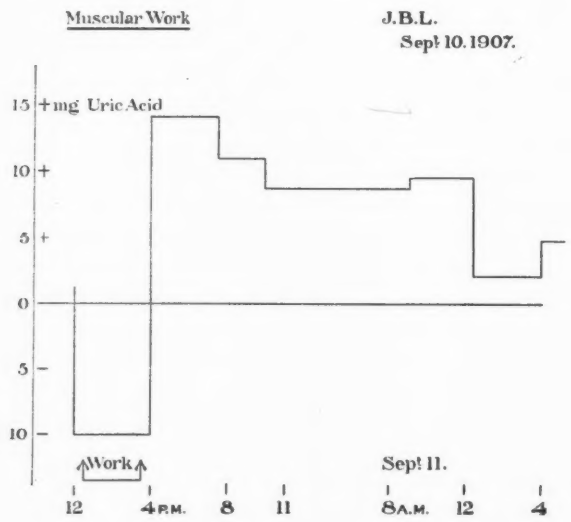

FIG. 4.

does not last longer than in these experiments, but is then maintained at a level considerably above the normal for many hours.[2] Lastly, Fig. 3 shows how the

[2] In Fig. 5, a point to which Burian first drew attention (*Zeit. f. Physiol. Chem.*, xliii. 533) is confirmed and illustrated. He states that muscular activity is followed by an increased

reaction to cold, when no voluntary muscular activity occurs, results in an increased output of uric acid that comes into full evidence during the exposure, and then is maintained for many hours after the abnormal loss of heat has been stopped.

What then is the nature of the processes the activity of which, as manifested by an increased uric acid output, is intensified by muscular work? The fact that the output during the work tends to be diminished, and especially the fact that the subsequent increase lasts for a time far longer than, as we have seen there is ground for supposing, could be accounted for by delay in excretion,

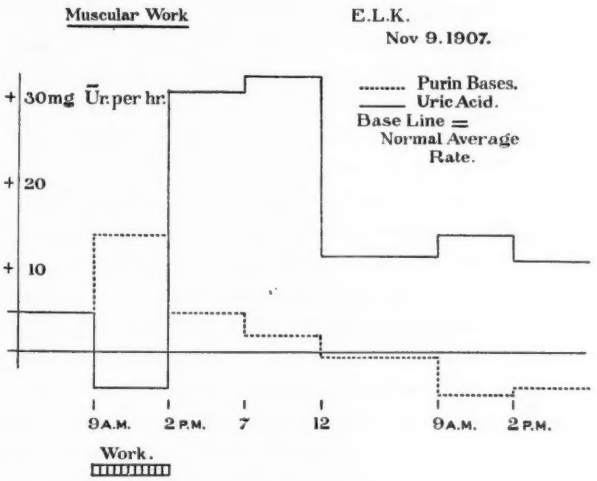

FIG. 5.

seems to exclude the probability of the activity concerned being the voluntary contractions of the muscles involved in the performance of the work. And yet when a change in the condition of the neuro-muscular system results in a change in the amount of excretory products of metabolism it is necessary to assume that these products are derived from the muscles till it is proved that that is not the case. We cannot leave the muscles out of account till, for instance, it is shown that the metabolism of muscles that are not at the time actually doing work may not be intensified by an antecedent period of activity in the form of work, the metabolism, for instance, that finds its expression in the constant condition of tonus; or, again, till we can say that the work has not led to an increased rate of decay in the fabric of the tissue that has been primarily affected by the work.

output of purin nitrogen, at first in the form of purin bases, subsequently in that of uric acid. The dotted line in Fig. 5 shows the course of the excretion of purin bases other than uric acid, the curve being referred to the normal average output represented at each period of the 24 hours as the horizontal base line. It is raised during the work, but sinks as the uric acid curve rises. The same point is illustrated again on Dec. 1 in the same series of experiments (Table X).

Till these possibilities are excluded there can be no warrant for ascribing the increased output of uric acid to any other tissue than the muscles.

The condition of muscles which are not actually doing work is not one of suspended animation; they are the seat of metabolic change, and, at any rate, one physical manifestation of this metabolism is the state of tonus which is characteristic of normal voluntary muscles, and is subject to variations that are regulated through the nervous system.

Then, again, we have seen that the effect of muscular activity on the output of uric acid is modified by the rate of heat loss and heat production. Muscular work is not commonly accompanied by such an acceleration of the rate of heat loss as to leave the body temperature unaffected; the net effect is to raise the body temperature: when this is the case the output of uric acid tends to be temporarily lowered. But when the rate of heat loss is abnormally great, then, in spite of the heat produced in the working of the muscles, the rate of uric acid production during muscular work may be increased. Again, when the rate at which heat is given off is increased, and compensatory heat production by voluntary exertions is not allowed to occur, then there may be a great increase in the output of uric acid, that occurs at once during the exposure to cold, and suggests that the reaction of the body to cold is a form of activity chemically indistinguishable from that which follows muscular work. In this reaction of the body to cold there are signs that the neuro-muscular apparatus is the seat of intensified activities other than voluntary contraction; shivering occurs, and this, as also the subjective feelings of briskness and the condition referred to as the bracing effect of cold, must have this significance. In fever, too, the rise of temperature is ushered in by signs of the same kind; the shivering fits are unmistakable evidence of an exaggerated activity in processes within the muscles quite different from those that manifest themselves in the voluntary contractions by which muscular work is carried out; and here, too, the output of uric acid is instantly increased. Other evidence of increased activity in processes within the muscles, different from those which show themselves in voluntary contraction, is found in the fact pointed out by Hale White that the axillary temperature on the paralysed side of a hemiplegic patient is often higher than on the sound side, although, as he has shown, in such a case the loss of heat may be greater on the paralysed side.

These considerations suggested that the normal diurnal variation in the output of uric acid, the minimum at night and rapid rise to a maximum in the morning hours, might be due to a tide in the activity of neuro-muscular functions, of which the tendon reflexes are a measure. During sleep reflex activity is at a low ebb; the rest of sleep gives rise to refreshed energy in such activity, and as the day advances the refreshing effect of sleep wears off. Curves of the variations in the intensity of the tendon reflexes were constructed by Lombard, which show precisely the character and form that such considerations would lead one to suspect, and the curves of diurnal variations in the output of uric acid have the form which would be required, if the principal variant cause in the production

of endogenous uric acid were such functions as those typified in the neuro-muscular phenomenon of the tendon reflexes.

We have endeavoured to test the influence of muscular activities of this kind by observations on the effect of doses of strychnin upon the output of uric acid. The experiments were as follows:—

1. Nov. 8, 1906. (v. Table IV.) 0·5 c.c. Liq. Strychninae Hydrochlor. was taken at 1 p.m., and again at 5 and 9 p.m., and at 9 a.m. the next morning. In the 24 hours immediately preceding the first dose the output had been 0·604 g., in the 24 hours following the first dose it was 0·629 g., and in the next 24 hours 0·596 g. No appreciable effect, with the exception of a slightly increased output during the night amounting to about 15 mg., was detected as a result of taking 20 mg. of the salt in four doses spread out over 20 hours.

2. Nov. 18, 1906. (v. Table IV.) 1 c.c. Liq. Strychninae Hydrochlor. was taken at 1 p.m., and again at 5 p.m.—20 mg. in two doses, with an interval of 4 hours. In the 24 hours preceding the first dose 3 doses of sodium citrate had been taken, each of 5 g., causing a high output amounting to 0·644 g.; in the 24 hours following the first dose of strychnin this was further increased to 0·671, and in the succeeding 24 hours the output was 0·675 g., of which, however, 25 mg. was, probably, due to the two hours' ride in a cold wind at the end of the period. The average 24 hours' output during the three weeks throughout which the diet was taken was 0·626 g., and these figures, for the 48 hours after the first dose of strychnin, were the highest observed at any time in the course of the experiment. The result is, however, open to the objection that the action of the citrate may have been in part responsible for some of the high rates in the first 24 hours.

3. Feb. 19, 1907. (v. Table VI.) The same subject took 1 c.c. of the same solution at 5 p.m., and again at 10 p.m., and on the next day also at 9 a.m. and 1 p.m. In the course of this day there were some subjectively perceptible signs of the action of the poison, 40 mg. having been taken in four doses spread over 20 hours. In the 24 hours preceding the first dose the uric acid excreted amounted to 0·507 g.; in the 24 hours during which the strychnin was taken, beginning with the first dose it amounted to 0·481 g., and in the next 24 hours to 0·573 g.—again the highest figure for any period of 24 hours in the course of this experiment.

4. Nov. 17, 1907. (v. Table X.) Another subject took at 12 and 5 p.m. 10 mg. of strychnin nitrate, and again the same dose at 9 a.m., 12 and 4 p.m., in all 50 mg. in five doses, spread over 28 hours. Symptoms of increased reflex excitability were noticed in the evening of the 18th. In the 24 hours preceding the first dose the uric acid excreted amounted to 0·389 g.; in the 24 hours, beginning 2 hours after the first dose, it rose to 0·490 g., but in the succeeding 24 hours, at the beginning of which the last dose was taken, it fell to 0·423 g. The average normal output in 24 hours during this experiment lasting more than 4 weeks was 0·429.

5. Nov. 23, 1907. (v. Table X.) This subject took again 3 similar doses

of the same solution of the nitrate of strychnin at 12, 3.30, and 8.30 p.m., and 2 more on the next day at 12 and 3.30 p.m. In the 24 hours preceding the first of these doses the output of uric acid had been abnormally high—0·476 g.—as the result of taking a large dose of sodium bicarbonate on the evening of the 21st. During the 24 hours after the first dose it was correspondingly low—0·349 g., but during the 24 hours beginning an hour and a half before the last dose it rose to 0·483.

In all these experiments, except the first where the dose was smaller and spread out over a longer period than in the others, a considerable dose of strychnin was followed by a marked rise in the output of uric acid.

Taking, therefore, all this evidence together, it seems clear that the voluntary muscles are the seat of activities other than voluntary contractions which set up metabolic changes that are characterized by an increased output of uric acid, and that some of the most striking variations in the rate at which endogenous uric acid is produced in the body are accounted for by these processes and traceable to the muscular system. The processes come markedly into evidence in the reaction to cold, and also in the rise of temperature in fever, and the facts suggest that thermogenetic processes in the muscles are prominent among the functions in the execution of which uric acid is produced.

If such a view of the origin of a considerable portion of the endogenous uric acid be adopted, it naturally occurs that evidence in support of it or to the contrary should be forthcoming from the study of the output of uric acid in various pathological conditions in which the neuro-muscular functions are abnormal. But a difficulty arises from the fact that the conditions that come in question are, with few exceptions, chronic, and not recovered from, so that it is not possible to obtain from the same individuals figures under normal conditions. All that it is possible to do is to determine the daily output per kg. of body weight, and compare this with the values obtained from normal individuals. But these latter, as the protocols at the end of this paper show, are very variable. In the following list is given the number of mg. of uric acid excreted daily per kg. of body weight on purin free diets on different occasions by normal subjects in our experiments:—

J. B. L.	Sept. 1906.	Insufficient diet . . .	6·2
„	Nov. 1906.	Abundant diet . . .	8·9
„	Feb. 1907.	„ „ . . .	7·1
„	May 1907.	„ „ . . .	7·5
„	Sept. 1907.	„ „ . . .	9·3
E. P. C.	May 1907.	„ „ . . .	4·0
E. L. K.	Nov. 1907.	„ „ . . .	5·9
H. S. R.	Jan. 1907.	„ „ . . .	7·4

From these figures it appears that there are very wide individual variations in healthy subjects, and that anything between 4 and 9 mg. per kg. may be

normal, and that even in the same individual on different occasions there may be variations amounting to nearly 50%. These facts make it difficult to argue from the figures obtained from a patient except when it is possible to make observations on him under normal conditions as well as abnormal, keeping the diet the same throughout.

Nevertheless, the figures furnished by Spriggs are of very great interest. Among the cases studied by him are two of tetanus: one of them was a man of about 82 kg. in weight who, while having spasms, excreted 10 mg. of uric acid per kg. per diem on a purin free diet, and later, when the spasms had passed off and the diet included fish and meat, excreted only 8 mg. per kg. This patient then excreted 25% more uric acid during the spasms, in spite of the fact that as he recovered he took more food, and food containing precursors of uric acid. The other case, a boy of 11, weighing 25 kg., excreted 20 mg. per kg. during his attack, which, as Spriggs points out, is probably excessive even at his age. No data are given as to the output normal for this subject on a similar diet after recovery.

Two cases of spastic paraplegia were also examined by Spriggs: one of them excreted 6 to 7 mg. per kg., the other 7 to 9. In both cases there seems to have been some suspicion of incontinence, which may cause the figures to be lower than they should, but in any case it is impossible to say that in regard to this condition they turn the scale either one way or the other, owing to the impossibility of getting controls.

On the other hand, Spriggs gives figures from cases in which, according to the results of our investigations, low values might perhaps be expected, but in which normal or even high values were observed. Thus, in a case of tabes with marked hypotonicity of the muscles, on three successive days the output was 9, 7, and 9 mg. of uric acid per kg., and in a boy of 4, with amyotonia congenita, it averaged 17 mg. per kg., when in another boy of the same age, who was normal, it was found to be 14 mg. per kg. Also in two cases of muscular dystrophy with remarkably low creatinin output the output of uric acid was high, ranging from 11 to 13 mg. in a boy of 16, and from 9 to 12 mg. in a man of 22; and in a case of myasthenia gravis also with a low yield of creatinin, the uric acid averaged 8 mg. per kg. daily. These last cases with loss of muscular power are perhaps less significant than the hypotonic cases, if we are right in associating the increased output of uric acid that we have found to follow muscular work, not so much with the work itself, as with the heightened muscular metabolism of other kinds that the work sets up for some time afterwards. And the significance of the cases of pathological hypotonicity may be regarded as emphasizing the difficulty that there is in defining exactly the relation between chemical change and functional activity. The fact that in health a particular form of chemical change is found to be associated with a particular form of functional activity does not imply, as a matter of course, that impairment of that function in disease must necessarily be associated with diminished chemical change. An efficiently working machine

requires oiling and fuelling in proportion to the rate at which it is worked, but a machine that is out of order does not necessarily take less oil and consume less fuel in proportion to its inefficiency. It is just in the disturbance of the normal ratio between effect on the one hand and friction and fuel consumption on the other that its inefficiency is made manifest. We are, therefore, we think, justified in attaching more weight to the positive evidence in support of our views supplied by Spriggs's cases of tetanus than to the negative evidence furnished by the other cases.

Spriggs himself is inclined, however, rather to associate the endogenous uric acid with visceral functions, without prejudice as to what the viscera concerned may be. Hirschstein more definitely ascribes as much as 70% of it to the activities of the digestive organs. This view, as pointed out before, is not in harmony with the view for which he contends in another part of his paper, but is based on the following evidence. He found that proteid food, as is well known, although free from purin compounds, causes more uric acid to be excreted the more abundant it is; that a patient in bed during one day and without food excreted considerably less than when taking food whether up or in bed; that purin bases may be found in the intestine of a dog, in undetermined but 'not insignificant amounts', three or four hours after an isolated purin free meal; and he cites the observations of Schittenhelm, who found purin bases to be present in human faeces when the diet was free from purin compounds, also in meconium, in the contents of a pancreatic cyst, and in the substance of the intestinal wall.

Our attention was diverted from the digestive organs as a probable seat of activities involving formation of uric acid in any considerable quantity for the following reasons:—

(1) The observation that complete abstention from food on one day, when the same amount of fluid was, however, taken, and at the same times as on the previous days, did not affect the form of the curve of uric acid excretion on that day. More particularly on that occasion, Sept. 22, 1906 (v. Table III), the morning rise was at least as well marked as usual. During the period ending at 4 a.m., the rate had been 8·1 mg. per hour; although the 7 a.m. meal was not taken, it rose in the period from 7 to 10 to 19·3 mg. per hour. The average rates for these periods on the four previous days had been 10·9 and 21·2 mg. per hour respectively. The lowest rate at any period on the 22nd was 17 mg. per hour. It is true that in the 24 hours from 7 a.m. on the 22nd to 7 a.m. on the 23rd the output was only 349 mg., when the average was 435, and that in the succeeding 24 hours it rose to 422 mg. But this fact seems to be less significant than the fact that the morning rise occurred as sharply, and the general form of the curve for the day was the same as when food was taken.

This seemed to show that the ordinary diurnal tide of uric acid excretion was independent of the activities of the digestive organs, though the forms of activity on which it does depend may, when no food is taken, tend to

be depressed. Hirschstein also notes that his patient, even on the day which was spent in bed and without food, excreted more uric acid during the morning than during the previous night.

(2) Hopkins and Hope found that isolated meals of non-nitrogenous food gave rise to no increased excretion of uric acid, although under these circumstances a definite leucocytosis could be observed, and although isolated meals of purin free nitrogenous food caused a definite increase in the rate of uric acid output.

(3) In the most marked changes in the rate of uric acid excretion that we were able to bring about experimentally, there was no reason to think of the digestive organs as being particularly concerned. In the experiments on the effect of fever, a strong disinclination for food was experienced, and it was only with difficulty that the ordinary rations could be taken. After muscular work no more food was taken than at other times, and there was no reason of which we were aware for thinking that the food was imperfectly dealt with before, or more perfectly after the work.

But although our attention was by these considerations, and the results of our experiments, turned in other directions, we do not pretend that the kinds of activity which we have found to be associated with the formation of endogenous uric acid are solely responsible for it.

Nevertheless, the few experiments which we have carried out expressly with a view to determining the relation of digestive activity to endogenous uric acid, have given results which are not compatible with the view that digestive activity is very closely related to its production. On a number of occasions the subjects of the experiments omitted to take the first meal of the day, taking instead the same amount of water as was usually taken in the form of milk. On four such occasions the result was that the usual morning rise in the rate of uric acid excretion did not appear, which at first sight suggests that this morning rise is the result of the activity of the digestive organs brought about by taking breakfast. But if that were so, the morning rise should be merely postponed, and should appear in due course after the first meal taken later in the day; but this was not the case. The output remained low throughout the day, although it was only the first meal that was dropped. The dates and figures were as follows:—

Sept. 21, 1907	8.30 a.m. to 12.30 18 mg. per hour instead of average 32	12.30–4.30 p.m. 14 mg. instead of average 30	
Nov. 16, 1907	9 a.m. to 2 p.m. 10 mg. per hour Average 23	2 p.m. to 7 p.m. 15 mg. per hour Average 21	7 p.m. to 12 13 mg. per hour Average 17
Nov. 20, 1907	11 mg. per hour Average 23	11·5 mg. per hour Average 21	7 mg. per hour Average 17
Nov. 29, 1907	12 mg. per hour Average 23	14 mg. per hour Average 21	12 mg. per hour Average 17

On the first and last of these days, Sept. 21 and Nov. 29, the subject

stayed in bed till the middle of the day when the first meal was taken, on the other two days he was occupied in the laboratory as usual. Other experiments (June 2, Sept. 29, and Nov. 30) showed that staying in bed, if breakfast was taken at the usual time, did not interfere with the occurrence of the usual morning rise of uric acid output.

On other occasions on which the first meal was omitted a different result was obtained: the rate of output rose in the usual way in the morning in spite of the fast:—

Sept. 27, 1907	8.30 to 12.30	12.30 to 4.30	4.30 to 8.30
	34 mg. per hour	26 mg. per hour	33 mg. per hour
	Average 32	Average 30	Average 31
Nov. 19, 1907	2 p.m.	7 p.m.	12 midnight
	24 mg. per hour	17 mg. per hour	17 mg. per hour
	Average 23	Average 21	Average 17

This result is, of course, equally, though in a different way, difficult to reconcile with the view that the morning rise signifies merely the return of the organs of digestion to activity. Why the results were in these two cases different from those referred to above we cannot with any confidence suggest. But on the two days before Nov. 19 considerable doses of strychnin had been taken, and the effect that we have observed this drug to have upon the output of uric acid may last for 24 hours. It is possible, therefore, that the result of Nov. 19 was the result of the action of the strychnin.

On Sept. 28, when active muscular exercise in the open air was taken before the first meal at 12.30, and on Dec. 1, when severe dumb-bell exercises for two hours were performed and no food taken till three hours after the work, the effects were those which muscular activity gave on other occasions when food had been taken.

It would seem, therefore, from these results, that the ordinary diurnal tide in the excretion of uric acid is determined by some form of activity other than that of the digestive organs, but some form of activity which is liable to be depressed if food is not taken at the habitual time.

Moreover, if we are right in associating the daily fluctuation in the rate of output of uric acid with a daily fluctuation in the activity of muscular functions, such as is indicated in the curve of variation in the intensity of the knee jerk obtained by Lombard and referred to above (p. 428), it may be noted that this latter curve, in addition to the main crest appearing in the early hours of the morning, shows minor ones shortly after each meal. It is possible for a function to be intensified by taking food and give rise to metabolic products in increased amount after food, without making it necessary to refer these products to the digestive organs as the seat of their formation.

The only other experiment at all bearing on this point was an indecisive one. On Nov. 27, 1907, 30 mg. of pilocarpin nitrate was taken in the evening. Sweating and salivation followed, but if there was any increased activity in other glandular organs it did not manifest itself in any marked departure from the normal figures for uric acid excretion. Possibly if the urine had been

examined at shorter intervals some more definite effect might have come to light.

The possibility of the involuntary muscular functions of the alimentary canal being in some way related to the formation of endogenous uric acid was tested on Sept. 23, 1907, by taking 0·5 g. of calomel at night. The purgation that followed, which was fairly sharp, was marked by no pronounced change in the output of uric acid, though there was a tendency for the figures to be low for more than 24 hours.

Some indication of the activity of other visceral functions than those of the secreting glands concerned in the digestion of food may be obtained from the excretion of nitrogen and phosphorus. The intake of nitrogen and phosphorus, though uniform throughout the day in all our experiments, was stopped for several hours at night. The food metabolism that results in the excretion of urea is, therefore, lowest in the morning, and rises with each meal to a maximum late in the day, or as shown in the experiment of November, 1906, and commented on in an earlier paper (Leathes), in the early part of the night during sleep. This curve is so entirely different from that for the excretion of uric acid, the maximum and minimum of the one coinciding approximately with the minimum and maximum of the other, that we feel great difficulty in associating the endogenous uric acid with the internal metabolic processes of viscera concerned in assimilation. The curve for phosphoric acid is, broadly speaking, similar to that for total nitrogen, the only noticeable point being that there is a tendency (November, 1907) for greater delay in the removal of superfluous ingested phosphorus than of superfluous nitrogen, so that the minimum rate of phosphorus excretion may occur after the rate of nitrogen excretion has begun to go up as a result of the morning meals.

The amount of phosphorus excreted in our experiments was large owing to the large amount of casein taken, and in so far as the fluctuations in the rate at which it was excreted indicate fluctuations in the intensity of visceral processes concerned with food metabolism, they do not point to uric acid being produced by these same processes.

When, however, we infer from the results which we have obtained, that there are metabolic changes in the muscles that are largely concerned with the production of uric acid, and that the daily fluctuations in the rate at which it is turned out bear no relation to the activity of digestive processes, we do not wish to imply that all the endogenous uric acid is derived from the muscles. But if the muscles are concerned and other organs as well, when the relative bulk of the muscles and the other organs of the body is considered, and also the small absolute amount of uric acid produced as a result of even the most intense activity of the muscles, it is not to be wondered at that only those variations can be detected which may be traced back to the voluntary muscles, forming as they do 40 % of the whole body.

There is another way in which the experiments we are recording show

variations to occur in the output of uric acid. Some of the series of figures given were obtained from the same individual, on the same diet, on different occasions: as the following list shows, the output varied considerably:

In Aug. 1906	the	average	output	in 24 hours was 610 mg.
„ Nov. 1906	„	„	„	626 „
„ Jan. 1907	„	„	„	560 „
„ Feb. 1907	„	„	„	500 „
„ May 1907	„	„	„	527 „
„ Sept. 1907	„	„	„	652 „

The low figures obtained in the early months of 1907 attracted attention at the time, and were hypothetically referred to the condition of the subject, who had been in town from August of the preceding year until the end of March, and attributed the fact that he was at the time more subject to catarrhs and sore throats than usual to this circumstance. It was a matter of interest, on this supposition, to see what the output would be in September after a holiday of six weeks in the mountains. The result that the average output was higher in this month than on any previous occasion tends to support the view that, other things being equal, the amount of uric acid excreted will be highest when the general health is best.

It is true that in February and May the diet contained 1 pint less milk than in the other four series, which means that about 10 % less proteid was taken daily, although the nitrogen intake and calorie supply were still abundant. Now diminution of the proteid in the food is accompanied, as is well known, by diminution in the output of uric acid. But in the experiment of Sept. 1906, when the nitrogen intake in the same subject was reduced not merely 10 % but almost 75 %, and the average daily nitrogen deficit from the urine analysis alone amounted to more than 2 g., the output of uric acid fell only to 450 mg.: this makes it extremely improbable that when it fell to 500 in February, the fall should be entirely ascribed to the fact that the proteid supply was 10 % below what it was when the output was 650 mg. There was some other factor to account for the low output in February and May, and that suggested in the previous paragraph is the one to which we are inclined.

Before concluding, there are some other particulars in our experiments to which reference may be made. The effect of a weak infusion of tea, and of a solution of 60 mg. of caffein taken at 7 p.m. on November 12 and 13, will be found in Table X. These drugs were tested because of the action which they, in common with other purin derivatives, have upon the muscles. On both occasions the output was low during the following night, but whether this should be referred to the drugs these isolated observations cannot decide. But, at any rate, on neither occasion was there any sign of an opposite effect at any time, and that was the point which we wished to test.[3]

[3] Krüger and Schmid, *Zeit. f. Physiol. Chem.*, xxxii, 104, found that as much as 200 mg. of caffein had no effect on the 24 hours' output of uric acid.

On November 14, in the same series, 14 g. of lactic acid was taken, dissolved in the necessary amount of soda at 7 p.m., with a view to confirmation of Wiener's experiments on the animal synthesis of uric acid. In the 24 hours beginning at midnight, the output was hardly above the average, though considerably above that for the preceding and subsequent 24 hours. Wiener found 10 g. sodium lactate to give a larger increase in a man than 17 g. did in our experiment. On November 21, the corresponding amount of sodium bicarbonate gave rise to an output in the following 24 hours increased, in comparison with that for the preceding 24 hours, as much as it had been when the lactate was taken. It would be difficult, therefore, to ascribe any increased output to the lactic acid itself.

Like sodium bicarbonate, sodium citrate (cf. November 18, 1906, Table IV) seems, as was found by Macleod and Haskins, to increase the amount of uric acid. But the action of salicylate of soda is on a different scale: 4·7 g. at 7 p.m. on November 25 (Table X) gave rise to the appearance within 24 hours of 0·77 g. when the normal average amount was 0·43. This has been observed before by many others (Jackson and Blackfan, Rockwood and Epps, and references in von Noorden's *Pathologie des Stoffwechsels*).

Potassium bromide, of which 10 g. was taken in the course of November 15, 1906 (Table IV) was found to have absolutely no effect on the output of uric acid.

Lastly, the long series of observations upon the excretion of creatinin calls for comment. No determinations of creatin were made. But the one remarkable feature about the excretion of creatinin is its extraordinary constancy. The only occasion on which there was any marked departure from the normal rates was during the fever of September 24, 1906 (Table III), which has been commented on in an earlier paper (Leathes). In some cases small increases were noted after muscular work: on September 10, 1907 (Table IX), an increase over the normal average for 24 hours of 0·14 g.: on the three days following the experiment of May 30, 1907 (Table VIII), the output was 1·57, 1·56 and 1·54 g. when the normal average was 1·49 g., and on May 11, 1907 (Table VII), an additional excretion of 0·12 g. after exercise was observed: on this occasion considerable quantities of additional fluid were drunk in the form of soda-water, about 1500 c.c. These variations are trifling compared with those affecting the uric acid under such circumstances. Also, in the six different series of observations on the same individual, including the experiments on a low nitrogen intake in September, 1906 (Table III), the output was remarkably constant at about 2·0 g.

CONCLUSIONS

1. A marked increase in the output of endogenous uric acid has been found to occur in three conditions: (*a*) Fever, (*b*) exposure to cold, (*c*) after severe exertions. The increased output coincides and terminates with the febrile rise of temperature, coincides with and outlasts by many hours the exposure to cold,

follows the exertions and lasts for many hours after them. It is suggested that in all these three conditions the uric acid has its origin in metabolic processes occurring principally in the voluntary muscles, and not immediately related to voluntary contractions and work.

2. The daily tide in uric acid excretion, high output in the morning, low output at night, is not due to retention of uric acid formed during the night; nor is it due to the fact that the digestive organs are inactive during the night, if that is a fact, with the last meal taken at 9 or 10 p.m., as in most of our experiments. It is rather due to the quickened activity of all functions, especially those of the voluntary muscles, which results from the rest of sleep.

3. Generally speaking, the more lively the performance of the functions of the body as a whole, the greater the amount of uric acid produced will tend to be.

Protocols. Tables III–X

Uric acid was estimated in the experiments given in Tables III and IV by Wörner's modification, in the rest by Folin's modification of Hopkins's method: the methods were checked against one another.

Creatinin was estimated by a modification of Folin's colorimetric method, which was checked against the method as carried out by Folin himself.

Total purin nitrogen in the experiments given in Table VII was estimated by the Camerer Arnstein method; in the experiments in Table X the estimation was carried out after filtering off the ammonium urate for uric acid estimation; the total purin nitrogen was then obtained by addition of the uric acid nitrogen.

Phosphoric acid was estimated by titration.

All the uric acid and creatinin estimations were done by the same worker (J. B. L.); the other estimations in Table VII and VIII and the first part of Table IX, all by E. P. C., and in the second half of Table IX and in Table X, all by E. L. K.

The experiments were all carried out at the Lister Institute for Preventive Medicine.

TABLE III

N. = g. Nitrogen excreted per hour. C. = g. Creatinin excreted per hour. U. = mg. Uric Acid excreted per hour.

Date. 1906, Sept.	ca. 4 A.M.			7 A.M.			10 A.M.			1 P.M.			4 P.M.			7 P.M.			10 P.M.			Total in 24 hours			ending	
	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	g. N.	g. C.	mg. U.		
14																						12·4	2·1	490	11.15 a.m.	[J. B. L.] Diet started 13th. Six meals at 7 and 10 a.m., 1, 4, 7, and 10 p.m., each of 90 g. 'Arrowroot' biscuits, 20 g. butter, 350 c.c. water. = ca. 35 Cal. per kg. and 5·7 g. N. per diem.
15																						8·9	2·0	432	10 a.m.	
16																						7·7	2·2	444	10.30 a.m.	
17										20	84	24	34	93	18	44	91	24	31	80	21	7·7	2·1	454	10 a.m.	
18	34	58	8	32	86	14	24	82	20	39	87	23	40	80	20	28	90	18	23	81	14	7·7	1·9	380	10 p.m.	
19	35	84	14	17	85	16	18	78	19	40	92	26	49	94	24	41	87	19	26	83	14	8·0	2·1	440	,, ,,	
20	31	74	9·5	22	85	13	22	86	23	31	94	27	32	94	23	37	94	18	22	85	15	7·0	2·0	392	,, ,,	
21	39	87	12	19	80	18	20	84	22	28	99	24	26	92	25	36	93	26	29	84	23	6·8	2·1	494	,, ,,	[usual.
22	42	80	8	25	74	18	22	83	19	32	79	18	27	84	17	31	88	20	28	77	17	7·5	1·9	366	,, ,,	No food taken this day: water as
23	32	68	8·5	32	75	8	37	67	11	59	83	25	48	84	19	51	88	18	30	82	17	9·7	1·8	348	,, ,,	
24	50	80	15	28	81	19	26	87	23	28	93	28	22	80	23	19	91	23	27	83	20	7·4	2·0	504	,, ,,	4·6 c.c. Typhoid Vaccine at 6 p.m. Fever during night.
25	48	95	38	41	95	28	23	82	24	32	87	28	32	95	24	[46]	102	27	[59]	100	25	9·8	2·2	707	,, ,,	Meals dropped at 4 and 7 p.m. Water as usual. Slept from 7 to 8.30 p.m.
26	49	88	17	22	84	9	23	80	17	39	86	27	45	86	22											
Average.	40	79	14	26	83	16	24	31	20	37	88	25	36	88	22	37	92	21	27	84	18	7·95	2·0	454		
Omitting 25th & 26th	38	76	11	25	81	15	24	81	20	37	89	24	35	88	21	38	90	21	27	82	18					
																			From 18th to 21st			7·44	2·0	434		

TABLE IV

N., C., U., as in Table III.

Date. 1906, Nov.	ca. 4 A.M.			9 A.M.			1 P.M.			5 P.M.			9 P.M.			12 midnight			Total excretion in 24 hours			ending at	
	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C .	U.	N.	C.	U.	g. N.	g. C.	mg. U.		[J. B. L.] Diet started Nov. 2. Four meals, at 9, 1, 5, and 9, each of 570 c.c. milk, 170 g. bread and 30 g. butter. = 56 Cal. per kg. and 22 g. N. in 24 hours.
5				47	79	21	69	95	35	80	102	37	78	93	29	89	86	25				12 p.m.	
6	82	71	18	33	58	22	66	87	32	81	100	35	83	94	27	74	82	26	17·7	1·98	629	,,	
7	89	79	19	53	73	22	85	81	34	92	92	31	72	83	24	68	80	22	18·2	1·96	625	,,	
8	78	83	19	46	78	21	62	97	35	75	86	28	61	82	22	55	76	21	15·6	2·03	585	,,	0·5 c.c. Liq. Strych. Hydrochlor. at 1, 5 and 9 p.m.
9	*84	*81	*23				79	83	32	100	89	30	77	82	25	68	76	19	19·6	2·08	633	,,	Do. do. at 9 a.m. *This sample collected at 7 a.m.; none at 9 a.m.
10	63	77	18	45	74	21	83	91	37	86	90	32				*79	86	25	18·1	2·01	618	,,	5 g. Sod. Citrate at midnight. *Sample from 5 p.m. till 12.
				7.30 A.M.			2 P.M.			6 P.M.			12 midnight										
11				74	72	23	62	81	32	100	93	34	75	84	22				18·2	1·94	637	,,	Urine slightly alkaline at 2 p.m.
12				76	73	18	62	—	29	95	—	30	65	—	25				17·5		622	,,	
13				71	—	21	61	—	32	70	85	32	69	77	24				16·3	—	641	,,	
14				74	77	20	68	77	36	96	84	33	76	88	25				18·4	1·94	664	,,	
15				78	80	18	66	84	35	74	77	28	71	82	24				17·1	1·95	623	,,	Pot. Bromide 2 g. at 9, 5 g. at 10.30, 3 g. at 4 p.m. = in all about 2½ drams.
	ca. 4 A.M.			9 A.M.			1 P.M.			5 P.M.			9 P.M.			12 midnight							
16	100	77	21	56	76	20	77	89	35	89	90	35	85	92	25	75	82	25	19·1	2·01	626	,,	
17	109	85	21	55	87	22	58	88	32	80	92	29	68	84	27	61	83	23	17·4	2·01	616	,,	5 g. Sod. Citrate at 5, 9, and 12 p.m.
18	134	80	27	61	72	23	66	82	33	78	84	34	64	83	28	77	79	29	17·6	1·91	679	,,	Urine alkaline till 5 p.m. 1 c.c. Liq. Strych. Hydrochlor. at 1 and 5 p.m.
19				*57	74	22	62	77	33	78	82	31	83	86	30	68	83	26	16·1	1·90	658	,,	* This sample collected from midnight till 9 a.m.
20	104	78	25	64	73	22	89	91	39	98	83	34	93	83	28	82	82	27	20·8	1·95	690	,,	Bicycling 20 miles from 10.30 to 12.30. Wind very cold.
21	90	75	17	52	68	18	66	81	29	76	81	30	75	83	25	87	77	21	17·5	1·87	563	,,	Very warm, mild day.
22	90	77	22	52	68	20	58	80	30	80	85	26	78	85	28	66	78	23	17·2	1·89	589	,,	do. do.
23	79	74	21	49	72	21	85	88	40	117	91	35	74	88	26	76	76	22	19·3	1·96	653	,,	Colder: dressed lightly in order to feel cold.
24	107	82	17	45	73	17	72	96	30				*81	92	25	55	75	23	17·2	2·00	544	,,	Bicycled gently 35 miles from 3 to 7 p.m.; not cold, but air very damp. * This sample collected from 1 to 7 p.m., and the next one from 7 p.m. to 12.
25	77	79	23	43	79	19	65	80	26	90	91	32							16·4	1·96	565	1 p.m.	
Average	95	78	21	50	73	21	71	85	33	87	89	32	76	86	27	73	80	24	17·8	1·96	626		

Average	95	78	21	50	73	21	71	85	33	87	89	32	76	86	27	73	80	24	17·8	1·96	626	

very damp. * This sample collected from 1 to 7 p.m., and the next one from 7 p.m. to 12.

TABLE V

N., C., U., as in Table III.

Date. 1907, Jan.	8 A.M.			1 P.M.			5 P.M.			11 P.M.						
	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	g. N.	g. C.	mg. U.	
26				70	85	32	101	81	34	58	74	23	16·3		551	[J. B. L.] Diet started Jan. 24. Four meals, at 9, 1, 5, and 9, each of 570 c.c. milk, 170 g. bread, 30 g. butter. = ca. 56 Cal. per kg. and 22 g. N. in 24 hours.
27	58	80	13	58	86	[27]	71	85	34	60	84	19	14·5	2·00	494	Naso-pharyngeal catarrh came on on 25th.
28	71	79	14	104	92	36	89	90	[*21]	58	84	21	19·0	2·05	466	Bicycling 2 hours, skating 1 hour: 10 a.m. to 1 p.m.
29	80	81	21	65	87	27	44	87	27	70	93	22	16·0	2·08	567	Moderate exercise and sweating indoors. * Sample collected from 2 to 7 p.m.
30	59	75	20	72	92	34	85	97	36	62	75	24	15·9	1·97	638	Recovering from effects of catarrh: sat in incubation room (T. 37° C.) from 12 to 5 p.m.
31	82	79	23	78	70	32	90	79	29	[92]	[122]	[37]	18·7		644	Diet changed at 8 p.m.
Average	70	79	18	69	85	32	87	87	31	61	84	22	17·1	2·02	560	

TABLE VI

N., C., U., as in Table III.

Date. 1907, Feb.	8.30 A.M.			2 P.M.			6 P.M.			11 P.M.			Total in 24 hours			ending at	[J. B. L.] Meals at 9, 2, 6, and 10, each of 430 c.c. milk, made up to 570 c.c. with water, 170 g. bread, and 30 g. butter. = ca. 51 Cal. per kg. and 19 g. N. in 24 hours.
	N.	C.	U.	N.	C.	U.	N.	C.	U.	N.	C.	U.	g. N.	g. C.	mg. U.		
14				89	133	39	100	122	28	59	88	17	18·2	2·54	511	8.30 a.m. 15th	Diet started this day.
15	66	93	10	62	113	22	88	99	19	63	107	20	15·4	2·31	396	11 P.M. 15th	Catarrh.
16	56	80	14	53	89	25	70	112	25	56	87	17	13·9	2·13	457	,, 16th	
17	72	82	21	58	91	27	70	94	23	55	89	16	15·6	2·10	529	,, 17th	Sore throat.
18	71	72	19	61	101	22	59	93	22	56	91	19	15·2	2·07	500	,, 18th	
19	64	85	19	69	116	25	86	121	22	54	93	18	16·5	2·45	509	,, 19th	1 c.c. Liquor Strychninae Hydrochloratis 5 p.m. and 10 p.m.
20	44	78	15	47	104	27	72	85	26	53	109	24	11·8	2·22	515	,, 20th	Do. do. at 9 a.m. and 1.15 p.m.
21	54	73	21	70	99	30	58	96	23	57	94	17	14·1	2·10	548	,, 21st	
22	70	82	19	84	102	28	84	89	17	60	87	17	17·7	2·18	492	,, 22nd	
23	73	91	12	68	106	22	75	98	23	70	100	21	17·3	2·34	426	,, 23rd	200 c.c. water taken at 1 a.m. and 5 a.m.
24	63	95	17	59	117	28	55	94	26	64	108	21	14·6	2·47	531	,, 24th	
25	59	83	16	59	94	27	69	107	28	60	103	21	14·6	2·24	520	,, 25th	
26	71	84	17	74	107	24	56	94	17	51	93	22	15·8	2·24	464	,, 26th	0·47 Sodium Urate at 11.30 p.m.
27	53	74	17	65	98	32	58	101	24	65	106	21	14·1	2·17	[532]	,, 27th	
28	78	109	23	71	112	28	63	123	27	55	89	17	16·5	2·59	[575]	,, 28th	0·47 Sodium Urate at 9 a.m.
March 1	66	92	18	62	109	24	58	98	24								
Average	64	85	17	59	100	26	70	102	23	58	96	19	15·4	2·28	500		

TABLE VII

N., C., U., as in Table III.

B. = mg. Purin base nitrogen per hour. T.P. = mg. Total Purin nitrogen per hour. P_2O_5 = mg. P_2O_5 per hour.

[J. B. L.] Meals at 8, 1, 6, and 10, each of 430 c.c. milk, made up to 570 c.c. with water, 170 g. bread and 30 g. butter.

Date.	7.30 A.M.						1 P.M.						6 P.M.						10.30 P.M.						Total in 24 hours					ending at
1907, April	N.	C.	U.	B.	T.P.	P_2O_5	N.	C.	U.	B.	T.P.	P_2O_5	N.	C.	U.	B.	T.P.	P_2O_5	N.	C.	U.	B.	T.P.	P_2O_5	g. N.	g. C.	mg. U.	mg. B.	mg. T.P.	g. P_2O_5	
29																									14·3	2·10	652				9 a.m.
May 1																									14·7	1·83	415	54	192	1·94	7.30 a.m.
2							60	80	23	1·9	9·6		53	88	24	0·8	9·0	128	60	84	14	3·4	8·0	153	14·3	1·84	432	20	165	2·64	,,
3	70	80	19	2·1	8·5	139	61	90	24	2·5	10·7	57	53	81	22	3·2	10·4	125	64	84	17	1·3	7·1	156	15·0	1·98	486	48	210	—	,,
4	65	80	16	0·4	5·9	117	58	87	23	2·8	10·4	64	64	88	21	1·1	8·2	128	54	85	16	2·0	7·5	97	14·7	2·02	453	34	185	2·48	10.30 p.m.
5	64	81	19	3·5	9·8	168	63	81	24	1·9	9·9	76	60	76	21	2·6	9·7	126	63	97	25	1·2	9·4	154	15·1	1·99	519	60	233	3·22	,,
6	69	76	21	[9·1]	[6·0]	144	58	89	29	1·6	11·5	71	55	85	25	0·9	9·3	143	55	95	22	0·6	7·8	165	14·7	2·03	572	[98]	[289]	3·12	,,
7	67	75	20	1·1	7·7	150	66	85	31	—	9·9	84	81	89	26	2·6	11·2	156	68	84	25	3·9	12·3	178	16·7	1·97	595	36	234	3·36	,,
8	65	77	18	0·8	7·0	113	58	87	30	1·3	11·4	62	67	84	23	0·5	8·3	138	72	80	26	0·4	9·0	164	16·0	1·96	565	19	207	2·79	,,
9	86	70	23	0·3	7·9	113	80	80	28	3·4	12·9	48	81	85	[22]	2·6	10·0	[136]	75	75	[19]	2·0	8·5	[89]	18·7	1·85	593	19	217	2·69	1 p.m.
10	64	72	[13]	1·0	5·4	[97]	56	85	[18]	1·9	7·8	[38]	62	84	[21]	1·5	8·4	[74]	73	84	[10]	4·5	7·8	[103]	16·5	1·90	[419]	41	181	[2·17]	,,
11	65	84	[20]	0·7	7·5	[84]	57	88	[12]	2·9	6·7	[34]	65	97	[20]	5·1	11·8	[67]	81	88	[20]	1·8	8·4	[92]	15·4	2·01	[438]	66	210	[1·75]	,,
12	69	94	[18]	[10·4]	[6·3]	[125]	58	96	[28]	2·8	12·1	[35]													16·3	2·17	[498]	[146]	[312]	[2·11]	,,
Aver.	68	79	19·4	1·0	7·5	135	61	86	25·5	2·3	10·3	66	64	86	23·3	2·1	9·6	135	66	86	20·7	2·1	8·6	152	15·8	2·05	527	39	205	3·03	

Diet started April 30. May 9: Rectal Temp. lowered 4° F. by cold sponging from 4.15 to 5.25 p.m.

May 11: Bicycled 30 miles between 2 and 6 p.m. Warmly dressed; warm day.

Average: Bracketed figures not counted in in averages, nor figures before May 2nd.

TABLE VIII

N., C., U., P_2O_5, as in Table VII. H_2O = c.c. per hour.

[E. P. C.] Diet began May 17. Six meals daily, at 7, 10, 1, 4, 7, and 10, each of 380 c.c. milk, 60 g. bread, 20 g. cheese, 10 g. butter. = ca. 45 Cal. per kg. and 21 g. N. per diem.

Date.	7 A.M.					10 A.M.					1 P.M.					4 P.M.					7 P.M.					10 P.M.					Total for 24 hours					ending at
1907.	N.	C.	U.	P_2O_5	H_2O	N.	C.	U.	P_2O_5	H_2O	N.	C.	U.	P_2O_5	H_2O	N.	C.	U.	P_2O_5	H_2O	N.	C.	U.	P_2O_5	H_2O	N.	C.	U.	P_2O_5	H_2O	g. N.	g. C.	mg. U.	g. P_2O_5	l. H_2O	
May 18																														11·8	1·34	272	1·91	1·21	8 a.m.
19													16·1	88	36	65	57	22	101	37	88	64	18·1	169	106	89	64	18·5	168	80	16·6	1·48	371	3·05	1·55	,,
20	61	59	11·2	127	40	55	69	13·0	80	33	57	61	13·6	119	39	70	63	15·1	172	43	81	66	14·6	212	61	86	62	9·1	196	109	16·2	1·50	335	3·27	1·26	4 p.m.
21	72	60	10·6	144	71	58	61	16·4	87	48	64	65	10·6	122	46	74	63	10·9	182	50	80	65	8·6	205	61	100	71	8·8	212	113	17·4	1·49	280	3·69	1·58	,,
22	71	55	6·8	138	63	69	64	15·9	96	49	71	61	11·1	134	56	75	64	10·0	196	45	83	65	10·5	198	66	96	65	9·6	189	94	18·2	1·46	225	3·77	1·54	,,
23	63	55	6·7	133	54	72	76	19·5	108	52	64	65	13·9	148	43	74	66	12·7	206	43	78	59	12·3	203	53	93	66	14·5	185	61	17·4	1·51	259	3·74	1·38	,,
24	75	60	10·9	139	65	62	63	11·9	78	39	63	64	10·7	122	40	69	64	7·9	176	51	84	56	19·5	190	54	90	58	21·1	—	51	17·7	1·49	270	3·55	1·31	,,
25	77	59	17·1	153	42	66	59	28·7	164	43	72	63	20·2	145	42	83	67	17·4	200	43	85	64	12·9	202	50	94	69	17·2	196	58	18·8	1·44	475	4·0 ?	1·08	,,
26	75	59	10·8	144	59	67	65	20·4	89	46	70	61	16·1	147	49	83	67	13·7	209	51	90	67	17·1	209	76	89	67	16·7	170	79	18·7	1·51	338	3·83	1·29	,,
27	75	57	8·0	145	63	58	64	17·6	75	43	57	66	13·2	131	41	63	55	14·7	183	47	77	67	6·2	159	51	88	61	20·4	80	60	17·6	1·48	312	3·64	1·43	,,
28	74	61	12·4	132	57	67	65	20·7	96	39	67	64	19·2	173	48	78	67	19·6	215	51	81	66	12·8	218	59	95	65	12·0	227	135	17·9	1·51	369	3·33	1·29	,,
29	72	57	10·2	161	67	58	63	20·1	95	44	66	64	16·4	164	51	69	67	14·6	210	50	76	67	12·7	215	67	86	70	19·0	206	76	17·6	1·49	314	4·20	1·62	,,
30	71	56	9·8	160	78	61	61	19·0	95	54	72	68	—	146	50	61	62	8·9	178	43	52	70	3·6	132	33	95	72	6·9	66	57	17·1	1·49	311?	3·93	1·58	,,
31	75	62	9·2	176	43	65	65	13·8	108	37	71	64	11·0	170	38	90	66	11·3	213	39	85	68	16·6	215	43	90	69	18·0	220	44	18·0	1·57	223	3·65	1·00	,,
June 1	78	62	14·2	167	39	66	63	17·8	87	39	71	69	13·9	146	39	77	69	16·1	227	45	87	65	12·1	219	50	96	71	13·9	188	66	18·6	1·56	375	4·19	0·98	,,
2	76	60	11·4	149	41	75	65	21·5	115	62	79	68	18·2	164	70	66	65	18·3	219	50	84	62	14·5	203	51	98	63	14·8	197	79	18·9	1·54	354	4·06	1·27	,,
3	82	57	10·7	192	75	62	61	19·9	84	44	72	63	12·7	137	54	85	67	9·1	215	83	86	63	17·7	223	63	102	60	15·5	189	90	19·4	1·46	309	4·34	1·63	,,
4	83	55	14·7	168	71	73	62	21·6	93	65	41	60	14·7	153	46	89	66	14·9	211	58											20·1	1·43	386	4·12	1·61	,,
Average of 16 days	74	58	10·9	156	58	66	64	18·6	97	46	68	64	14·5	142	46	75	65	13·9	195	49	81	64·5	13·1	204	59	93	66	14·7	186	78	18·1	1·49	321	3·89	1·37	
Average from 20–24th			9·2					15·3					12·0					11·5					11·5					13·0				274			

May 24: Swimming bath 2.50—5.35 p.m. Rectal T. down from 101·6° to 98·5°. May 27: Exercise stripped and cold 4.10—6.50 p.m. Rectal T. down from 101·8° to 99·8°.
May 30: Exercise in heavy clothing 3.10—5.50 p.m. Rectal T. up to 103·2°. June 2: In bed till 12.15. Meals as usual.
June 3: Swimming bath 2.50—5.30 p.m. Rectal T. down from 101·2° to 98·8°.

TABLE IX

N., C., U., P_2O_5, as in Table VII.

Date.	8.30 A.M.				12.30 P.M.				4.30 P.M.				8.30 P.M.				11.30 P.M.				Total in 24 hours ending at 12.30 p.m.				
1907, Sept.	N.	C.	U.	P_2O_5	N.	C.	U.	P_2O_5	N.	C.	U.	P_2O_5	N.	C.	U.	P_2O_5	N.	C.	U.	P_2O_5	N.	C.	U.	P_2O_5	
2					59	83	31	37	61	82	20	104	65	83	21	147	72	83	29	152			499		[J. B. L.] Diet began Sept. 1. Four meals, at 8.30 a.m., 12.30, 4.30, 8.30 p.m., each of 570 c.c. milk, 170 g. bread, 30 g. butter. = ca. 56 Cal. per kg. and 22 g. N. per diem.
3	78	75	19	112	55	84	19	38	80	85	26	134	76	82	26	181	83	82	21	152	16·5	1·93	499	2·62	
4	73	76	12	105	60	85	28	41	78	86	23	117	75	79	19	155	75	85	23	176	17·7	1·94	492	2·82	
5	79	78	22	124	63	86	31	47	68	88	29	136	77	89	26	157	81	89	23	167	18·0	2·02	539	2·92	
6	78	75	22	117	56	88	25	38	82	84	30	151	88	86	28	166	76	77	24	139	17·5	1·94	589	2·87	2 hrs. 40 mins. at swimming bath till 4 p.m.
7	77	75	23	123	60	82	32	56	70	86	31	147	82	87	26	208	76	86	19	182	18·5	1·96	643	3·02	
8	75	72	18	123	63	83	22	54	75	91	31	146	86	89	27	173	71	87	27	125	17·6	1·98	537	3·29	
9	65	76	22	116	59	88	34	62	73	88	32	157	76	88	30	211	90	85	31	185	16·8	1·99	645	2·94	
10	73	72	23	116	74	82	33	54	53	86	[20]	60	67	96	45	65	69	87	38	167	18·2	1·97	685	3·28	Hard work with two 10 lb. dumb-bells 1.30—[4.30 p.m.
11	67	80	31	158	68	83	41	77	78	89	32	169	99	89	35	225	110	87	28	198	15·6	2·04	816	2·73	
12	78	78	24	127	64	82	36	87	71	83	31	141	75	83	23	183	85	84	29	187	20·1	1·97	719	3·66	
13	83	78	21	139	70	82	[41]	70	95	88	[47]	177	95	86	[56]	236	101	84	[49]	227	18·7	1·98	659	3·39	173 g. sweetbread at 9 a.m.
14	86	70	[35]	146	71	83	[42]	53	72	82	33	151	75	82	25	155	86	80	[29]	181	21·3	1·88	[1051]	3·86	173 g. sweetbread at 8.30 p.m.
15	92	68	[46]	150	62	86	[54]	63	82	79	[51]	159	85	81	[41]	176	87	78	[41]	174	19·2	1·85	[943]	3·36	
16	76	[74]	24	93	58	86	36	41	72	88	38	146	81	90	33	184	90	87	28	143	18·5	[1·95]	[851]	2·87	
17	77	75	22	121	59	83	28	55	78	86	28	150	72	82	26	166	97	82	21	139	18·1	1·93	672	3·04	
18	84	74	23	128	62	75	26	44	80	83	30	126	84	86	30	190	83	92	25	167	19·0	1·91	589	3·01	
19	77	74	23	115	74	—	37	59	66	—	[24]	99	81	89	31	103	82	83	26	168	19·0	—	673	3·04	Work with 3 lb. dumb-bells 1.30—4.30 p.m.
20	79	75	22	126	74	84	33	66	66	84	28	165	73	84	28	205	94	84	27	214	18·5	1·94	624	2·71	
21	84	76	24	142	81	74	18	63	49	78	14	58	71	86	27	155	70	81	27	201	19·1	1·87	593	3·65	Stayed in bed till 12.30. No food till 12.30.
22	75	73	23	143	67	70	34	72	80	83	34	186	95	80	28	169	66	72	22	145	16·4	1·81	585	3·03	
23	67	75	21	128	71	79	36	90	104	86	36	169	107	83	29	206	95	73	19	194	17·8	1·89	643	3·38	0·5 g. Calomel at 11.30 p.m.
24	79	72	17	113	55	85	30	50	60	82	24	140	70	87	28	213	86	87	24	248	20·6	1·93	585	3·30	
25	80	72	20	145	60	81	30	69	87	84	33	188	91	89	35	228	93	79	31	192	17·4	1·91	585	3·64	
26	86	75	25	137	74	84	36	60	63	—	29	148	93	—	36	281	106	—	32	178	20·8	—	733	3·72	Three hours in room at 37° C. from 1.30 to 4.30.
27	89	—	26	146	73	—	34	60	55	—	26	59	71	86	33	145	80	80	31	189	20·3	—	725	3·54	In bed till 12.30. No breakfast till 12.30.
28	81	70	27	147	56	76	29	73	56	77	35	118	105	79	47	196	128	80	43	203	17·0	1·79	694	3·00	Bicycling 10 a.m. to 4.30 p.m. No breakfast till
29	79	[64]	24	143	83	—	34	45													20·4	—	806	3·30	Breakfast at 8.30. In bed till 12.30. [12.30.
Average	78	74	22	127	65	82	32	57	72	84	30	134	82	85	31	180	86	83	27	176	18·3	1·93	652	3·14	

TABLE X

N., U., B., T.P., P_2O_5, H_2O., as in Table VII.

[E. L. K.] Diet began Oct. 30. Three meals daily, at 9 a.m., 2 and 7 p.m., each of 750 c.c. milk and 230 g. bread. = ca. 44 Cal. per kg. and 22 g. N. per diem.

Date.	9 A.M.						2 P.M.						7 P.M.						12 P.M.						Total for 24 hours ending at 12 P.M.					
1907.	N.	U.	B.	T.P.	P_2O_5	H_2O	N.	U.	B.	T.P.	P_2O_5	H_2O	N.	U.	B.	T.P.	P_2O_5	H_2O	N.	U.	B.	T.P.	P_2O_5	H_2O	g. N.	mg. U.	mg. B.	mg. T.P.	g. P_2O_5	c.c. H_2O
Oct. 31			1·8	6·3			58	19·1	2·8	9·3			61	21·6	3·9	10·2			64	17·2	2·1	7·2			14·3	527	60	190		
Nov. 1	63	12·8	—	—		35	82	26·4	—	—		125	79	19·9	—	—		81	62	16·4	—	—		36	16·9	428	—	—		1·52
2	73	15·4	3·4	8·5		37	57	18·5	2·3	8·7		38	125	30·1	4·6	14·7		115	80	18·9	3·1	9·4		42	19·7	476	81	236		1·31
3	79	15·4	3·1	8·2		40	88	20·8	3·7	10·7		78	91	19·2	4·7	11·1		72	102	23·6	2·6	10·4		74	21·1	456	83	235		1·48
4	70	13·6	2·1	6·6		42	78	19·5	3·4	9·9		84	90	18·9	4·0	10·3		90	76	15·1	2·5	7·5		43	18·5	390	68	200		1·46
5	77	13·5	2·2	6·7	149	38	98	23·9	4·3	12·3	66	70	103	21·8	3·5	10·8	162	68	91	19·1	2·9	9·3	219	45	21·3	445	73	222	3·58	1·25
6	85	12·5	2·8	6·9	138	42	100	17·1	3·0	8·7	66	85	99	23·0	3·0	10·7	152	81	90	17·0	2·6	8·3	193	47	22·1	398	68	201	3·29	1·45
7	77	12·8	1·6	5·8	126	39	51	25·8	3·1	11·7	109	75	93	20·2	2·9	7·6	150	47	100	19·2	2·0	8·4	213	44	19·2	441	54	201	3·50	1·18
8	76	15·3	1·8	6·9	131	31	96	27·9	2·1	11·4	89	47	105	23·9	1·9	9·9	144	52	86	17·1	2·6	8·3	194	40	21·2	482	50	211	3·31	0·98
9	82	17·6	2·7	8·6	131	34	41	19·4	8·0	14·5	25	19	109	50·2	5·5	22·3	113	51	113	47·0	4·3	20·0	213	47	20·8	758	109	362	3·03	0·91
10	88	23·7	2·5	10·4	118	33	84	36·4	2·3	14·4	98	37	107	31·4	2·5	13·0	182	46	98	27·7	2·5	11·7	208	41	22·3	689	59	289	3·51	0·92
11	77	19·0	2·2	8·6	122	32	98	34·3	3·4	14·8	59	71	105	26·3	4·5	13·3	172	88	90	15·8	3·3	8·6	198	70	21·6	553	76	260	3·23	1·43
12	48	10·0	3·3	6·6	109	40	100	22·9	6·2	13·9	71	113	101	14·3	6·7	11·4	154	146	110	8·9	7·4	10·3	187	84	19·9	321	131	238	3·05	2·07
13	43	6·2	2·1	4·1	111	41	89	17·2	6·3	12·1	62	127	70	22·3	3·9	11·4	172	93	88	14·8	3·8	8·7	191	57	16·2	326	88	197	3·13	1·75
14	75	8·9	3·7	6·7	114	55	93	26·3	2·5	11·3	66	81	98	22·2	3·0	10·4	163	83	92	10·0	4·4	7·7	237	79	20·8	373	83	207	3·36	1·71
15	66	12·7	2·3	6·5	119	42	88	25·7	4·2	12·8	66	71	99	23·7	4·6	12·5	161	82	87	16·3	4·0	9·5	187	48	19·8	443	86	234	3·15	1·39
16	72	14·0	2·2	6·8	122	37	83	10·2	6·2	9·6	62	201	71	14·8	3·5	7·7	105	80	80	13·3	3·0	7·4	179	52	18·2	318	83	189	2·83	2·02
17	62	12·8	1·9	6·2	121	34	87	26·7	3·2	12·1	75	59	92	25·6	3·2	11·7	178	54	91	18·5	3·6	9·7	188	47	19·1	469	67	224	3·29	1·10
18	79	14·3	3·1	7·9	115	39	95	28·3	3·5	12·9	93	68	101	24·0	3·4	11·4	174	64	83	14·8	2·8	7·7	181	42	21·1	460	76	229	3·23	1·23
19	74	12·5	2·7	6·9	119	40	80	24·0	3·2	11·2	68	49	98	19·0	4·0	10·4	188	77	95	17·0	4·4	10·1	171	58	20·1	415	82	220	3·14	1·27
20	75	11·8	2·9	6·9	111	47	81	10·6	8·5	12·0	59	165	64	11·5	4·3	8·1	93	76	52	7·1	3·5	5·8	106	34	16·6	252	108	191	2·30	1·78
21	69	12·8	3·2	7·5	108	56	79	18·9	2·6	8·9	98	57	83	18·0	2·7	9·0	157	52	87	17·8	2·9	8·8	180	49	18·7	388	70	199	3·15	1·29
22	71	14·0	2·3	7·0	99	37	92	25·7	3·4	12·0	66	81	77	22·5	4·3	11·8	151	80	83	18·3	2·2	8·3	189	44	19·0	459	70	223	2·92	1·36
23	75	14·4	2·0	6·6	117	42	88	23·3	2·7	10·5	62	92	96	13·4	5·4	9·8	120	121	88	12·5	4·3	7·5	167	70	20·4	376	80	205	2·80	1·78
24	58	11·4	1·9	5·7	133	34	72	23·3	2·5	10·3	98	50	100	25·1	3·5	11·8	184	64	90	12·6	3·3	9 2	193	47	18·4	433	64	208	3·57	1·11
25	80	15·0	2·9	7·9	122	42	91	26·9	4·4	13·4	71	89	101	21·7	4·3	11·5	177	97	91	23·1	4·5	12·3	172	85	21·4	494	93	257	3·40	1·73
26	79	36·2	3·0	15·1	180	83	70	38·2	3·3	17·0	72	48	91	27·4	4·0	13·1	160	54	91	16·4	4·6	10·0	150	51	19·7	739	86	332	3·54	1·55
27	75	2·8	3·5	4·5	123	39	76	12·9	2·7	7·0	79	44	90	18·5	4·2	10·3	181	54	90	18·8	2·7	8·9	189	48	19·6	277	82	174	3·35	1·08
28	75	14·5	3·1	8·0	115	53	78	20·2	3·5	10·3	65	60	58	10·2	3·1	6·5	100	54	130	20·1	5·3	12·0	254	107	20·1	383	88	216	3·13	1·58
29	75	8·9	3·5	6·5	123	60	94	11·9	5·6	9·6	73	204	63	13·8	3·9	8·5	107	61	78	12·0	3·3	7·3	151	28	18·3	270	96	186	2·76	2·00
30	64	11·3	1·8	5·5	118	60	83	25·4	3	11·4	69	96	89	21·7	3·8	11·1	174	77	83	18·7	2·9	9·2	184	64	18·5	431	65	208	3·20	1·73
							[1]41	4·8	8·8	10·4	26	11																		
Dec. 1	62	12·5	2·5		119	39	[2]54	32·0	10·1	20·7	26	10	83	48·1	3·7	19·8	53	40												
Average	72	12·8	2·6	6·9	123	43	86	23·3	3·4	11·1	73	82	91	20·7	3·9	10·8	153	74	88	16·6	3·5	9·0	188	54	19·7	429	75	218	3·18	1·45

Average is from 21 normal days. Nov. 7: Walk from 10 a.m. to 2 p.m. Nov. 9: Severe muscular work 10 a.m.—3 p.m., sawing and chopping wood. Nov. 12: 500 c.c. infusion of 3 g. tea with 7 o'clock meal. Nov. 13: 500 c.c. solution of 0·06 g. caffein with 7 o'clock meal. Nov. 14: 500 c.c. solution of 14 g. lactic acid neutralized with soda with 7 o'clock meal. Nov. 16: 9 o'clock meal omitted, 750 c.c. water taken instead; cold day. Nov. 17: 10 mg. Strychnin nitrate at 12 and 5 p.m. Nov. 18: 10 mg. Strychnin nitrate at 9, 12, and 4. Nov. 19: 9 o'clock meal omitted, 750 c.c. water taken instead. Nov. 20: 9 o'clock meal omitted, 750 c.c. water at 9 instead; no meal at 7, one at 12 p.m. instead. Nov. 21: 9·25 g. $NaHCO_3$ in milk at 7 p.m., 250 c.c. water afterwards. Nov. 22: Urine alkaline till 7 p.m. Nov. 23: Strychnin at 12, 3.30 and 8.30 p.m. Nov. 24: Strychnin at 12 and 3.30 p.m. Nov. 25: 4 g. Salicylic acid neutralized with soda in 250 c.c. water at 7.30 p.m. Nov. 27: 0·03 Pilocarpin nitrate at 9.15 p.m. Nov. 29: Stayed in bed till 1 p.m.; 700 c.c. water at 9, no milk or bread. Nov. 30: Stayed in bed till 1 p.m.; breakfast as usual. Dec. 1: 700 c.c. water at 9 a.m., no milk or bread. Two 10 lb. dumb-bells raised from floor to above head 1,000 times between 9.30 and 11.30 a.m.

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Nov. 18: 9 o'clock meal omitted, 750 c.c. water taken instead. Nov. 20: 9 o'clock meal omitted, 750 c.c. water at 9 instead; no meal at 7, one at 12 p.m. instead. Nov. 21: 925 g. $NaHCO_3$ in milk at 7 p.m., 250 c.c. water afterwards. Nov. 22: Urine alkaline till 7 p.m. Nov. 23: Strychnin at 12, 3.30 and 8.30 p.m. Nov. 24: Strychnin at 12 and 3.30 p.m. Nov. 25: 4 g. Salicylic acid neutralized with soda in 250 c.c. water at 7.30 p.m. Nov. 27: 0·03 Pilocarpin nitrate at 9.15 p.m. Nov. 29: Stayed in bed till 1 p.m.; 700 c.c. water at 9, no milk or bread. Nov. 30: Stayed in bed till 1 p.m.; breakfast as usual. Dec. 1: 700 c.c. water at 9 a.m., no milk or bread. Two 10 lb. dumb-bells raised from floor to above head 1,000 times between 8.30 and 11.30 a.m.

THE RESPIRATORY MOVEMENTS IN HEMIPLEGIA: A CASE WITH TRACINGS SHOWING THE MOVEMENTS OF THE TWO SIDES, AND THE PECULIAR EFFECTS OF COUGHING, AND A CYRTOMETER TRACING SHOWING PECULIAR CHANGES IN THE SHAPE OF THE PARALYSED SIDE OF THE THORAX

By SAMUEL WEST

Hughlings Jackson in 1893 described peculiar changes of the respiratory movements in hemiplegia, which led him to develop a theory of the nervous mechanism of respiration which differs from that usually held. The normal respiratory movements are of two kinds, ordinary and voluntary.

The *ordinary* are chiefly diaphragmatic, at any rate in the male.

The *voluntary*—or *forced* as they are often inaccurately called—are chiefly costal.

In hemiplegia there is a difference between the movements of the two sides, which is different for the two kinds of breathing. Thus, in ordinary breathing the movements are increased on the paralysed side, especially in the upper part, while in voluntary breathing they are increased on the sound side. In many cases the difference is obvious, in others it is slight and requires looking for, and in some it is absent. These observations have been confirmed by many writers.

Judson Bury examined a large number of cases and found the changes described in 60 per cent.

Pierce Clarke found them present in every instance in 161 cases, without relation to age, character, duration, or severity.

Weissenburg stated that in nearly every case of the 160 examined, he was able to confirm Hughlings Jackson's observations. The movements, however, varied greatly in different patients, and sometimes the difference was hardly perceptible. He also stated that at the end of ordinary or quiet respiration the chest on the sound side had a longer range of movement, and retracted more, than on the paralysed side, so that with the exaggeration of inspiration there was a defect of expiration.

Boeri examined 61 cases and found the difference obvious in 49 but absent in 12, i. e. in nearly 20 per cent.

[Q. J. M., July, 1908.]

We may therefore conclude that the differences described are usually present, though not invariably.

It may be that the duration of the disease is important, and that though present at first the difference may gradually disappear in the course of time. I have indeed observed this in one case.

A man of 45 years of age developed embolic hemiplegia on the right side while under observation. The difference between the two sides was well marked at first. As the patient improved, although the hemiplegia persisted the movements of the chest became perfectly symmetrical, and this was confirmed by tambour tracings.

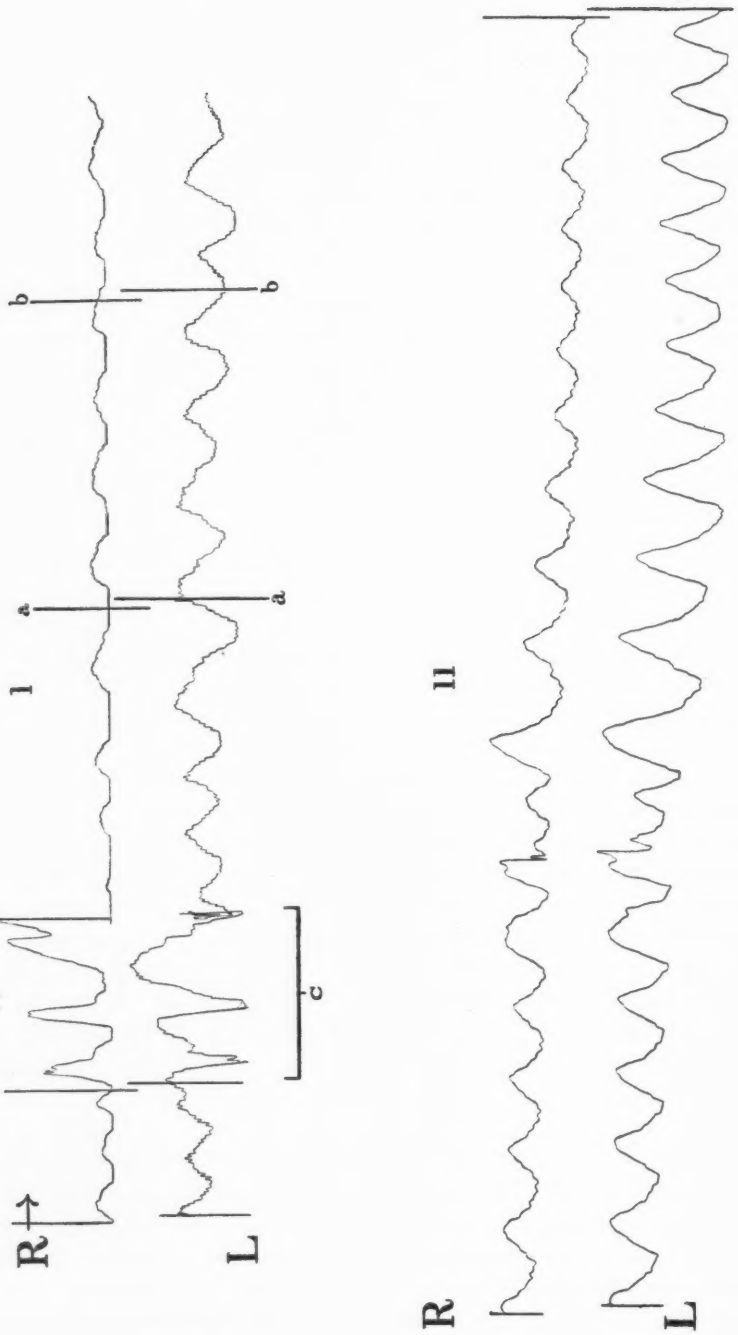
These being the facts, Hughlings Jackson suggested the following theory to explain them. *Ordinary breathing* is an automatic act governed by the respiratory centre in the medulla. The respiratory centre is double, each side being controlled or inhibited from higher centres on the opposite side of the brain. *Voluntary breathing,* as its name would imply, is of cerebral origin, and controlled by centres on the opposite side of the brain, the impulses being sent down to the respective centres for the associated movements of the larynx, ribs, and diaphragm, in the same way as they are sent to the centres for the movements of the arm or leg. With voluntary breathing the respiratory centre has nothing to do. It is in fact put out of gear or inhibited for the time being, so that the impulses from the brain pass by or evade it.

There are thus two sets of respiratory fibres passing from the brain—the one inhibitory, or controlling, to the opposite half of the respiratory centre in the medulla; the other direct, evading the respiratory centre and running the same course to the spinal centres for the respiratory movements as the ordinary motor fibres do to the centres for other movements. Both sets of fibres would be affected by the lesion which produced the hemiplegia. The inhibitory fibres being damaged, the opposite half of the respiratory centre would be under diminished control, and therefore the movements of ordinary breathing on the paralysed side would be exaggerated. The damage to the direct fibres would prevent the passage of voluntary stimuli to the groups of respiratory muscles, as it would to the rest of the muscles of the paralysed side, and thus the voluntary movements of respiration would be diminished—diminished only, and not completely abolished as in the limbs, because, according to Broadbent's theory, in the case of such closely associated bilateral movements the centres of both sides would be actuated from either side of the brain.

The following case shows many points of interest, and is instructive :—

Malignant endocarditis—right hemiplegia—great diminution of respiratory movements on the paralysed side both for ordinary and voluntary breathing —remarkable effects of coughing—curious flattening and change of thoracic curve on paralysed side.

Autopsy. Malignant endocarditis and other secondary lesions—clot in


R
L
I
a
b
a
b
c
II
R
L

middle cerebral artery, occluding Sylvian artery and also lenticulo-striate artery—medulla normal.

Thomas G., aged 32, was admitted to the Hospital suffering with malignant endocarditis. One month after admission he woke up one night and told the nurse he could not move his right arm. He was found to be completely hemiplegic on the right side; the face however was but slightly affected, and speech was only so far involved that articulation was a little thick and indistinct. The patient was perfectly conscious throughout, and understood everything that was said to him. The hemiplegia continued unchanged, but the patient rapidly ran downhill, and died about three weeks later.

Post mortem, besides the malignant endocarditis and concomitant lesions, the middle cerebral artery was found plugged, the thrombus occluding not only the Sylvian artery but some of the central branches as well, especially the lenticulo-striate artery. The medulla was normal.

The case, which presented many peculiar features in respect of the malignant endocarditis, was of especial interest during life on account of the *peculiar modification of respiration.*

As the patient lay in bed upon the back, the right, i. e. the paralysed, side was flatter all over the front than the other, and moved but little on respiration. The difference between the two sides was very obvious to the eye and hand in ordinary breathing, and was greatly increased in voluntary breathing.

Coughing produced the most extraordinary effect, for while the sound side contracted, the paralysed side bulged or was blown out. This gave a most curious sensation to the hand laid upon the side.

The diaphragm moved apparently equally on the two sides, and an X-ray examination made the following day seemed to confirm this.

With the assistance of Dr. Langdon Brown an apparatus was arranged with two tambours, and by this means synchronous tracings of the movements of the two sides were obtained, thus giving a graphic representation of what was seen and felt.

Tracing 1 shows the curves obtained with the tambours placed just outside the nipple on the two sides, the upper being that from the right or paralysed side, the lower from the left or sound side.

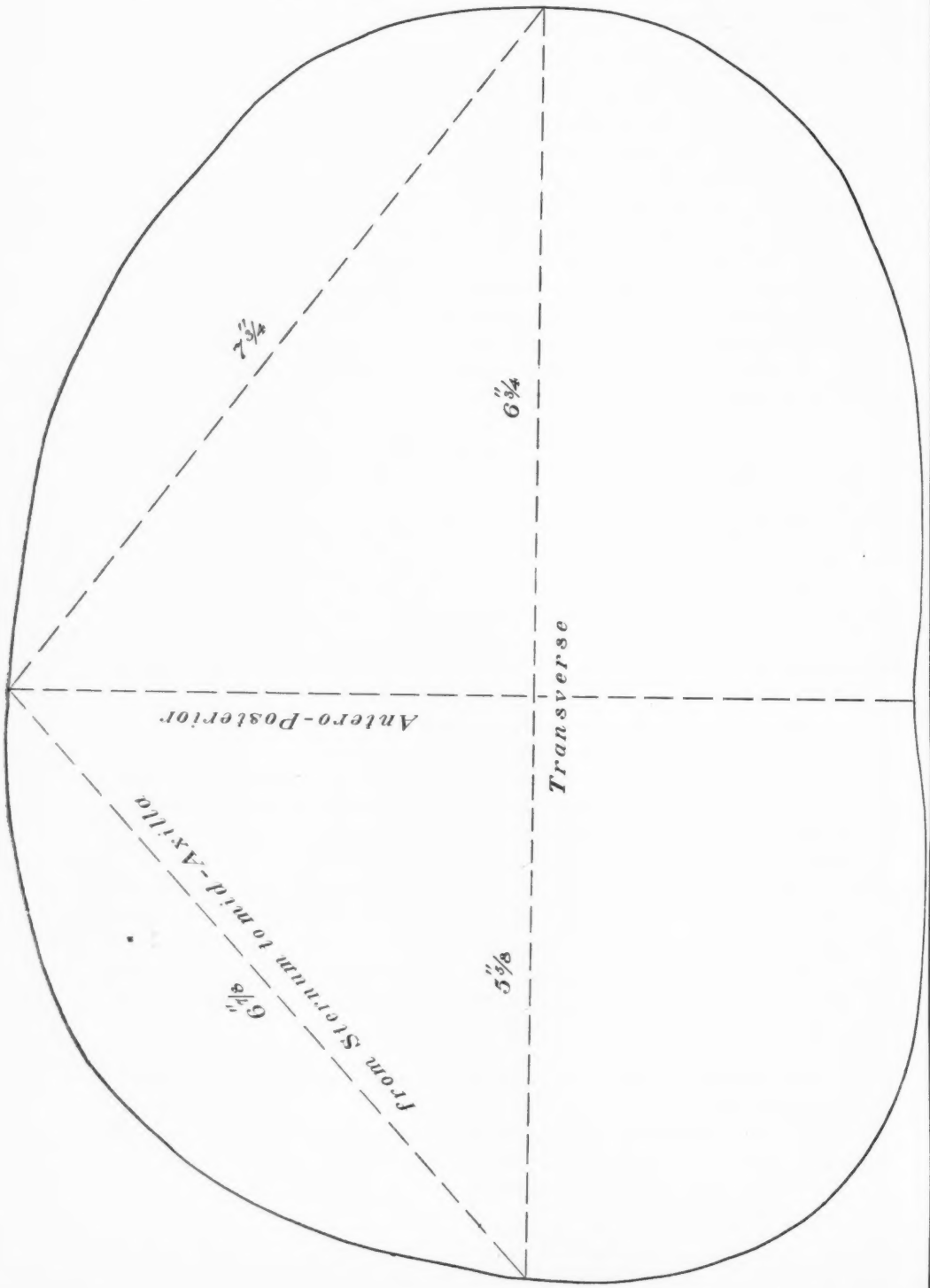
The middle part (*c*) shows the effect of coughing; on each side of this part the curves are those for ordinary breathing. The lines *a* and *b* mark the parts of the two tracings which correspond.

In *ordinary breathing* the following peculiarities are observed on the paralysed side.

1. The respiratory excursion both inspiratory and expiratory is much diminished, i. e. the height of the wave is reduced.

2. The character of the wave is altered.

(*a*) It is much rounder.


7¾"
6¾"
Antero-Posterior
Transverse
From Sternum to mid-Axilla
6⅛"
5⅝

(*b*) It is delayed, for the rise may not begin till that on the sound side is three-fourths to five-sixths complete.

(*c*) It is shorter, so that the post-expiratory pause, which hardly exists on the sound side, is very obvious.

In *voluntary breathing* the differences are of the same kind but exaggerated.

On *coughing* (*c*) the curves move in opposite directions, for while on the sound side after somewhat exaggerated inspiration the chest contracts, on the paralysed side instead of contracting it is distended by the cough, and the more powerful the cough the greater the distension or bulging.

Tracing 2 was taken two inches above the level of the umbilicus in either hypochondrium, and surprised us by showing clearly that, though the diaphragm appeared to the eye and hand to be moving equally on the two sides, it was not doing so really but moved distinctly less on the paralysed side. The waves however were synchronous, and their character and time the same on the two sides.

This case, so far as voluntary breathing is concerned, agrees with Hughlings Jackson's statements, but in respect of ordinary breathing is opposed to them, for the movements are less and not greater on the paralysed side.

The effect of coughing was very remarkable and has not, I believe, been previously described and demonstrated.

The change in the shape of the paralysed side is also, I think, new. The great flattening which was so obvious has been referred to. The cyrtometer tracing showed something more, for with the flattening from back to front was associated a widening from side to side, the difference in the transverse measurement of the two sides being more than an inch, viz.—

Right side (paralysed) $6\frac{3}{4}$ inches.
Left side (sound) $5\frac{5}{8}$ inches.

From this we may conclude that the rounded shape of the normal chest is largely due to the action of the intercostal muscles, and that when they are paralysed the side falls in. Probably the actual shape would have varied with position, but the patient was not well enough to admit of the experiment. The tracing given was taken with the patient lying flat on the back.

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PRIMARY MALIGNANT DISEASE OF THE VERMIFORM APPENDIX[1]

By ROBERT GRAHAM ELWELL

With Plate 39

Introduction

The occurrence of primary malignant disease of the vermiform appendix was first suggested by Merling in the year 1838, as an explanation of certain pathological appearances which he found in an appendix during a post-mortem examination.

At that time the importance of the appendix in relation to abdominal disease had not gained recognition, and therefore Merling's report excited but little interest. An interval of twenty-seven years elapsed before a second case was reported; but after the year 1865 the records became more numerous.

The earlier reports were mainly based on post-mortem examinations; the symptoms which preceded the death of the individual were not generally detailed, and the nature of the growth was not verified by the microscope. These records, therefore, while possessing a certain historical interest, are of little value from a clinical or histological standpoint.

The introduction of the microscope, an extended knowledge of pathology, and the development of abdominal surgery led to the more frequent publication of cases which satisfy the requirements of modern criticism; but for some time the literature consisted of little more than isolated reports. In 1897 Letulle and Weinberg attempted to correlate chronic obliterative appendicitis with the incidence of new growths in the appendix, but no extensive discussion of the subject appeared until 1903. In that year three papers were contributed in rapid succession by Claude, Elting, and Moschcowitz, in which the respective authors supplied new cases and reviewed the previous records. Their treatment of the literature was *comprehensive rather than critical*, and permitted the inclusion of several doubtful cases, but they were able to establish very definite conclusions in regard to the clinical aspect of their subject.

The first complete analysis of recorded cases was effected by Rolleston and Jones in 1905. Their researches necessitated the exclusion of all cases published before 1882. In many of the excluded cases microscopic examination had not been employed, while in others there was evidence to show that the growth had

[1] This paper was originally presented as a Thesis for the M.B. degree in the University of Cambridge. The author is indebted to Professor A. E. Barker for kind permission to publish the case now recorded for the first time.

[Q. J. M., July, 1908.]

originated in the caecum. But even after the strictest revision of the records they were able to present forty-two cases which they could accept as instances of primary malignant growth of the appendix. These, and other more recent cases, may at first be considered together without regard to their precise histological classification, since when viewed in this way they present certain points of interest.

A study of the literature leads to the conclusion that the cases first reported were found at autopsy, while those more recently recorded were discovered at operation undertaken for relief of inflammatory conditions. This point of difference can be associated with the increased surgical activity of the present day, and is otherwise of little significance; but it may be further noted that both the post-mortem cases and those derived from the operating theatre present examples of new growth in an early stage of development.

From the history of medicine, it appears that most diseases have been first identified in their more advanced stages, and their initial or early manifestations have been recognized by the efforts of subsequent observers. With primary malignant disease of the appendix it is not so; in most of the accepted cases the growth, though pronounced, after microscopic examination, to be highly malignant, was discovered before any manifestation of its malignancy could be recognized by the clinician. This singular fact has been explained on the supposition that the growth, owing to its peculiar position, very readily induces inflammatory complications, which lead to its removal before it can infiltrate surrounding structures or give rise to secondary deposits. Such an explanation is, however, not wholly convincing, since if the obscurity which enshrouds the advanced manifestations of primary malignant growths in the appendix were entirely due to the activity of modern surgeons, some light should be obtainable from the autopsies of an earlier period. It appears, however, that the growths discovered by the pathologist were not more malignant in development than those removed by the operator, and the discovery of the growth in either case was generally accidental.

In estimating the influence of surgical intervention in checking the development of new growth in the appendix, it must be remembered that in a large proportion of cases operated on for inflammatory conditions, the appendix itself is not removed, and therefore if a growth were present it could develop and give rise to further symptoms. Two cases are recorded in which malignant disease was discovered after the evacuation of an appendix abscess. In one (Case 12) there was extensive involvement of the caecum, ileum, and colon, beyond the appendix, where the growth was supposed to originate; in this case death occurred six months after the original operation. In the other (Case 9) the appendix alone appeared to be directly invaded, though there were metastatic deposits in the retro-peritoneal glands; this patient survived the original operation for three and a half years. In both cases there was a history of a persistent sinus following the operation.

It has also been supposed that where operative interference has not been

employed death has supervened from inflammatory complications before the growth has had time to betray its malignant character. Inflammatory complications do not, however, appear to be inevitable, for growths have been reported in five individuals (Cases 1, 2, 6, 7, 8) who died from other causes without having manifested any symptoms suggestive of a lesion in the appendix. It is also true that many patients (Cases 18, 23, 29, 33) who eventually underwent operation gave a protracted history of recurrent appendicitis before the growth was removed; but such histories can be of little value until the relation of the new growth to inflammatory conditions is precisely determined. Much more important in this connexion is the fact that of the eight cases (Cases 1–8) discovered at autopsy, one only (Case 5) can be found in which death was directly attributable to the inflammatory complications of the growth.

It may be inferred that, although in most instances primary growths of the appendix are associated with inflammatory conditions which attract the attention of the surgeon, in a small proportion of cases they betray no concomitant symptoms. In both groups the behaviour of the growths is at striking variance with their histological appearance.

Although modern operative measures may not be held accountable for the comparative innocence of primary malignant disease of the appendix, they are largely responsible for its more frequent recognition. When attention has been drawn to any morbid condition, the recorded cases become progressively more numerous; but the increased incidence of primary growths in the appendix is correlated with the more systematic examination of appendices removed at operation for the relief of inflammatory conditions.

The question whether these cases betray a comparatively frequent but unrecognized cause of appendicitis, or appear as the outcome of chronic inflammation, cannot now be determined. Cases (34 and 35) can be quoted in which a growth was found at operation during the first acute attack; but the numerous cases (17, 23, 29, 33) which give a protracted history of inflammatory symptoms appear to favour the view, advanced by Letulle and Weinberg, that chronic obliterative appendicitis tends to give rise to new growths. It is certainly noteworthy that these growths most commonly occur at that very period of life during which the individual is most liable to inflammatory conditions of the appendix, but generally exempt from the invasion of carcinoma.

Consideration of the relationship between malignant growths and inflammatory conditions of the appendix necessitates allusion to appendicular concretions of stercoliths. These bodies are regarded as chronic irritants, and have been suggested as factors in the causation of malignant disease, on the analogy of gall stones in connexion with carcinoma of the gall bladder. But since they are recorded in four cases only (15, 41, 27, 42) they appear to be comparatively as unimportant in connexion with malignant disease as they are in connexion with inflammation of the appendix.[2]

Although the accepted cases of primary malignant disease of the appendix

[2] *Vide* Kelly and Hurdon, *Diseases of the Vermiform Appendix*, 1905, p. 362.

do not number more than fifty, so various a nomenclature has been employed in the report that a concise classification of the tumours is impossible unless many of the terms are discarded.

For this reason the table at the end of this paper has been compiled with the object of reproducing, wherever possible, the exact descriptions given by the individual authors. Thus the necessity for retaining the different terms employed to designate the tumours is largely obviated.

The nomenclature would be greatly simplified if the following classification could be adopted:—

(*a*) Endothelioma. (*b*) Sarcoma. (*c*) Carcinoma.

(*a*) Endothelioma. The restrictions which should limit the use of this term are indicated on p. 468.

(*b*) Sarcoma. Of this growth one type—the round-celled sarcoma—is recorded in four cases (49, 50, 51, 52). It would appear that the comparative innocence of other growths in the appendix does not characterize these tumours.

(*c*) Carcinoma. Two types of carcinoma (as suggested by Rolleston and Jones) should be recognized:—(i) the columnar cell, (ii) the spheroidal cell. It would be gratifying to find that all cases of carcinoma which show a definite columnar cell formation could be traced to an origin in the caecum. But in one case (9) where columnar cell growth is reported the caecum does not appear to have been invaded.

Report of Case.

A case not previously reported will now be described and compared in its clinical and histological features with other recorded cases.

Clinical. *Summary of Case.* The patient, a male, aged 17, was admitted to University College Hospital on July 17, 1905, under the care of Mr. Barker.

History. In July, 1904, the patient was seized for the first time with pain in the lower part of the back, chiefly on the right side. The pain was sudden in onset, sharp in character, and aggravated by exercise to a degree so severe as to confine the patient to bed. The first onset was marked by headache, vomiting on a single occasion, and constipation. Rest in bed and hot flannels to the abdomen caused the pain to subside for a time. The pain recurred, however, at intervals of about a week during a period of two months; each recurrence was signalized by the act of vomiting.

In March, 1905, the patient had a second attack. On this occasion the pain was referred to the right iliac region and down the front of the right leg. Vomiting, headache, and constipation occurred as before. Between the months of March and July in 1905 the patient had three further attacks; two of severe and one of milder degree.

The family history contained no important detail.

When admitted the patient had a temperature of 99·8° F., a pulse of 120

per minute; the tongue was coated. The patient was anaemic, but not cachectic or wasted.

Abdominal examination revealed tenderness and rigidity in the right iliac region; at this point was felt a small, resonant, gurgling, slightly mobile mass which did not fluctuate. Rectal examination was negative.

At the operation, which was performed by Mr. Barker, the appendix was found to be thickened, inflamed, kinked, and bent under the caecum in the form of a loop. In this position it was maintained by adhesions.

The adhesions were divided, the appendix when freed was amputated, the stump was covered in, and the abdomen completely closed.

The patient made an uneventful recovery.

PATHOLOGICAL. *Macroscopic appearance of appendix.* The appendix was five inches in length, thickened, inflamed, and invested by adhesions. The inflammation was most marked round the distal extremity, which contained a small stercolith. Two inches from the end of the appendix was a small, firm nodule which involved more than half the circumference of the appendix. There was thickening of the peritoneum, but no ulceration of the peritoneal surface over the nodule or elsewhere. The lumen of the appendix was reduced but not obliterated by the nodule. The mesappendix was normal. On section the mucous membrane was nowhere ulcerated. It presented a grey colour in the distal three inches. The nodule, already mentioned, was white in colour, fairly definite in outline, but not encapsuled. The lumen of the appendix contained a quantity of mucus and débris.

Microscopic appearance of the growth. Sections[3] were taken transversely across the appendix in order to include both the lumen of the organ and the growth.

The lumen of the appendix was occupied with a mass of inspissated mucus and débris. The surrounding mucous membrane contained a number of Leiberkühn's glands, which for the most part presented a normal appearance. The submucosa was considerably thickened by the deposition of fibrous tissue, but this area of fibrosis did not extend through half the circumference of the appendix.

Throughout the remainder of the circumference the muscular coat was separated from the mucous membrane by a very wide layer of tissue. In this layer the original structure of the part was lost, and was replaced by masses of cells in various stages of formation and degeneration; the masses were disposed in the form of alveoli separated by bands of fibrous tissue.

The tissue which presented this alveolar arrangement was regarded as the new formation; it was separated from the thickened submucosa by a strand of fibrous tissue which extended from the deep surface of the muscular coat and swept inwards round the margin of the tumour, but became indefinite at a point

[3] A considerable part of the tumour was utilized for the preparation of frozen sections; unfortunately therefore the whole tumour was not available for the complete series of sections which would be necessary to establish the point of departure of the growth.

where the cell masses had approached most nearly to the mucous membrane. At this point the irregularity of Lieberkühn's glands and the proximity of the alveolar masses suggested a possible site of origin for the growth.

A collection of small round cells could be traced along the fibrous strand where it marked the limit of the submucosa; but the rest of the section was remarkably free from round cell infiltration. The alveolar spaces were irregular and varied somewhat in size; at no point did they exhibit a lumen or any indication of glandular arrangement.

The cells which occupied the alveolar spaces varied widely in their appearance and arrangement in different parts of the section. For purposes of description they were regarded as passing through three stages. These distinct stages are reproduced in the accompanying microphotographs, but in the original section all intermediate grades were discernible:—

Stage 1. The alveolar spaces nearest to the mucous membrane are of considerable size, and are occupied by densely packed small round cells.[4] The individual cell outlines are in some cases indistinct. In each cell is a large circular nucleus surrounded by a finely granular protoplasm. Both cell protoplasm and nuclei are deeply stained.

Stage 2. The alveoli are separated by strands of fibrous tissue which form a more open network than in the previous stage. The intra-alveolar contents have undergone a marked change. The small round deeply-staining cells are replaced by large cellular areas, which exhibit a faint polygonal outline and contain well-stained nuclei.

The material of which these cellular areas are composed stains very faintly, and presents a homogeneous appearance. It is difficult to determine whether each individual polygonal area represents a single swollen and degenerate cell or the coalescence of several cells. At the margins of some of the alveoli the small deeply-staining cells are very closely congregated.

Stage 3. In the transition from stage 2 to stage 3 there is a gradual diminution in the size of the alveolar spaces, and a corresponding increase of fibrous tissue. The polygonal cell spaces gradually shrink, and assume a more definite outline. The homogeneous cell material is diminished or absent, and the nuclei are less numerous, less distinct, and appear in some places to be laterally compressed.

In the final stage the alveolar contents appear as shrunken, structureless masses attached to the alveolar margin only by very fine threads. At one or two points the shrunken masses show numerous dark interlacing fibres, between which are compressed the surviving nuclei and remains of cell protoplasm.

The muscular and serous coats outside the tumour are thickened.

In one portion of the section, between the muscular coat and the peritoneum, is a small pear-shaped mass of cells, which resembles those described in stage 1.

[4] The empty spaces seen in some of the alveoli probably originate in the preparation of the specimen.

The base of this mass rests on the peritoneum, the apex extends into the muscle. At another point, both muscular and peritoneal coats are involved by a small mass resembling advanced grades of stage 2 and stage 3.

Conclusion as to Nature of Tumour.

The main points in the microscopic appearances may be summarized:—

(1) The submucous layer is chiefly affected; the muscular coats are also invaded, but to a much slighter degree. The mucous membrane is closely approached at certain points, but it is not possible to identify the site of origin of the growth.

(2) The amount of round cell infiltration in all layers is comparatively small; but there is an increase of fibrous tissue, especially in the submucosa.

(3) The muscularis mucosae cannot be identified.[5]

(4) The arrangement of the growth is alveolar. The cells occupying the alveoli are originally small, round, or polyhedral, and contain large darkly-stained nuclei. There is no lumen in any alveolar space; and no columnar cells can be seen.

(5) The growth has no capsule, though at one point it appears to be limited by a strand of fibrous tissue.

(6) The process of growth is slow; evidence of this is afforded by the extensive deposition of fibrous tissue and the changes discernible in different parts of the growth.

(7) The changes alluded to appear to indicate a process of degeneration, which at one stage suggests colloid degeneration.

On these grounds it is concluded that the tumour resembles the type of growth known as spheroidal cell carcinoma, and that it is undergoing degenerative changes.

Comparison of the Present Case with those Previously Recorded, from the Clinical and Histological Standpoints.

Clinical. The case now reported bears a close resemblance to the majority of previously recorded cases. The details of this resemblance need no elaboration, but three main points may be noted:—

(1) The age of the patient.
(2) The possibility of diagnosis.
(3) The result of operation.

Age. The early age at which malignant growths occur in the appendix has been emphasized by every writer who has contributed to the subject. Rolleston and Jones institute an interesting comparison between growths originating in the appendix and those which occur elsewhere in the alimentary canal. They give 30·8 years as the average age for all types of growth in the appendix, and

[5] This adds to the difficulty of localizing the starting-point of the tumour.

also show that the age incidence varies with the type of growth. There is no doubt that the peculiarity of age incidence is mainly associated with the growth known as the spheroidal cell carcinoma. The youngest patient in whom such a growth is recorded was a girl aged eight (Case 40). A review of the other cases supports Baldauf's conclusion that they occur most commonly in the third decade, and suggests that the appendix is most liable to carcinoma at that period of life during which the other tissues of the body are most immune.

Diagnosis. In considering this question the cases may be divided into two classes:—(1) Cases in which the growth found at autopsy excited no suspicion during life (Cases 1, 2, 6, 7, 8). (2) Cases in which the growth was associated with symptoms of some inflammatory condition. Of the second class of cases one (Case 5) went to autopsy as 'a case of peritonitis of obscure origin'; two (Cases 9 and 12) underwent operation for the relief of persisting sinus after evacuation of an iliac abscess; in seven female patients (Cases 42–48) operation was undertaken for the relief of suspected pelvic lesions; two cases (3 and 4), details of which were derived from a post-mortem report, probably presented symptoms of inflammation during life, though there is no record to that effect. All the remaining cases were operated on for the relief of an inflammatory condition of the appendix, and in no instance was a correct diagnosis made before operation. New growths originating in the appendix have never been diagnosed before operation, because they do not present a distinctive clinical picture. Moschcowitz, after a careful study of the symptomatology in the recorded cases, was unable to demonstrate any pathognomonic feature; and it is now known that the presence of these growths is indicated only by the associated symptoms of inflammation. The wasting and cachexia which commonly accompany malignant disease do not occur in these cases,[6] and the degree of anaemia which has been noted in some instances may be attributed to chronic septic absorption. The tumours do not give any local signs which could lead to their identification; they are so small that they cannot be detected by palpation, they are very rarely accompanied by free fluid in the peritoneum (Cases 11 and 36), and since they are not in the direct line of passage of the intestinal contents they do not give rise to intestinal obstruction.

Result of operation. The result of operation in the case now recorded was quite satisfactory; the patient made an uninterrupted recovery, and has so far exhibited no indication of recurrence or metastatic infection. The presence of a new growth in the appendix does not appear to affect the immediate prognosis;

[6] Case 11 is an exception. This case is regarded by Rolleston and Jones as an example of primary spheroidal cell carcinoma of the appendix. The growth exhibited a degree of local and metastatic malignancy which is in striking contrast with the innocent behaviour of other growths reported as primary spheroidal cell carcinomata. It differed also in histological appearance from other spheroidal cell carcinomata examined by Rolleston and Jones. There is some doubt as to the site of origin of this growth, but every case with a marked local malignancy would be open to question on this point, and the growth, whatever its origin, is certainly distinct from those growths which are referred to as 'spheroidal cell carcinoma of the appendix'.

the extent of the associated inflammatory condition is a more important factor than the growth which, provided that it is limited to the appendix, contributes nothing to the risk of operation.

In four instances death occurred shortly after the operation, but in none of these cases did the growth correspond to the primary spheroidal cell carcinoma. In one case (50) which was reported as a round cell sarcoma a portion of the caecum was removed with the appendix. In two other cases operation was undertaken for the relief of a sinus persisting after the evacuation of an appendix abscess. In one (Case 9) of these the growth was regarded as a columnar cell carcinoma, and was confined to the appendix, but the patient was enfeebled by persistent septic infection for three and a half years; in the other (Case 12) a very extensive resection of the large and small bowel was necessary, and it cannot be conclusively shown that the growth originated in the appendix. The fourth case (10) presents several features which differentiate it from other cases in the literature: the patient was 63 years of age, and the growth, which showed little local invasive tendency but displayed an active metastatic malignancy, was composed of cylindrical, columnar, and polyhedral cells.

The ultimate prognosis after operation is extremely favourable; and although much of the evidence on this point is negative in character, it is rendered more valuable by the reports on cases 16, 21, 25, 30, 33, 37, which have been kept under observation. There is only one recorded instance of recurrence in which it is possible that the growth was confined to the appendix at the time of operation. As this case (13) has previously escaped comment it may be now considered:—The patient, a man aged 27, underwent operation for relief of appendicitis, from which he had first suffered four months previously. At the operation it was noted that the appendix was thickened, firm, and almost milk-white in appearance throughout its length. The appendix was removed, but a small stump was left. It is stated that the caecum appeared to be normal and no glands were observed. The patient was discharged when apparently convalescent, but was re-admitted three months later. He then gave a history of severe pain and rapid loss of flesh. He presented a cachectic appearance, his abdomen was distended with ascites, and he had metastatic deposits in his left subclavicular glands and in his abdominal wall. A laparotomy was performed, the ascitic fluid evacuated and a large mass discovered, which was fixed and nodular and involved the caecum, ascending colon, and neighbouring peritoneum. The patient improved after the laparotomy and he was sent home, presumably to die. The growth had obliterated the normal mucosa and filled the submucosa up to the muscular layers. It consisted of irregular polyhedral cells, with large round or oval vesicular nuclei, occasionally nucleoli, and a very fine rim of protoplasm. The cells were densely packed in larger or smaller masses, or more frequently arranged in the form of anastomosing columns—amid which were dilated blood capillaries and a few strands of connective tissue. The growth was regarded as a carcinoma. The nodule

from the abdominal wall presented the same microscopic appearance. In this case the growth was extremely malignant, and in this respect it is only equalled by Whipham's case (11). The age and initial symptoms of the patient afford some resemblance to the cases recorded as spheroidal cell carcinoma of the appendix; in all other respects the contrast is most marked. But the question arises, which must arise in all cases of advanced local malignancy, as to the site of origin of the growth.

It would be easy to maintain the innocent nature of tumours in the appendix, by assigning all growths which have invaded local structures to the caecum; and, therefore, to suggest that a growth originated in the caecum is unjustifiable without some trustworthy evidence.

In the present instance it may be noted that the caecum was stated to be normal at the first operation on macroscopic evidence only, while of the sections taken at different levels in the appendix all revealed the presence of new growth on microscopic examination. There were no naked-eye appearances which could indicate the limit of the growth and so determine the line of amputation.

In other cases (Ruyter) where recurrence has been reported the caecum has been subsequently regarded as the more probable site of origin for the tumour. The prospect of recurrence is not influenced by the character of the cells composing the growth; simple amputation appears to be equally effective in all cases where the growth is definitely restricted to the appendix.

In some cases glands have been removed from the neighbourhood of the appendix—but subsequent examination of these glands showed that the enlargement which occasioned their removal was due to inflammatory processes. The researches of Jamieson and Dobson showed that some of the lymphatic glands, more especially those which drain the tip of the appendix, pass directly to the upper ileo-colic group of glands situated on the duodenum. In the case of actively malignant growth, therefore, removal of the glands in the immediate neighbourhood of the appendix would not suffice to arrest the progress of the disease.

Histological. In presenting a series of alveoli, filled with masses of spheroidal cells, the tumour in the case now reported conforms to the type of new growth most commonly found in the appendix. Baldauf, in his conclusions, states that the most common type of growth in the appendix is the simple alveolar carcinoma, the next in frequency is the adeno-carcinoma, while the colloid carcinoma occurs most rarely. By 'simple alveolar carcinoma' he probably means the spheroidal cell carcinoma as described by Rolleston and Jones. These authors divided the growths into two main types: the columnar cell and the spheroidal cell carcinomata. Such a classification greatly simplifies the study of this subject, and is sufficiently comprehensive if made to include the growths which exhibit a transition from the columnar to the spheroidal cell.

When the identity of the growth has been established, attention may be given to the formative or degenerative changes which it undergoes. Of all

degenerative changes the form which is known as colloid degeneration is the most prominent. The use of the term 'colloid' for purposes of classification is undesirable, since it may lead to the inclusion of widely different growths, or, as in Rokitansky's four cases, to the inclusion of simple cystic distension of the appendix. Elting's inference that 'the colloid type is the most frequent', and the statement of Kelly and Hurdon that 'colloid carcinoma is found in a somewhat larger percentage of the cases of carcinoma of the appendix than obtains for the intestine as a whole', may have been based on this misapprehension. From a survey of the accepted cases it must be concluded that primary growths very rarely undergo colloid change. Elting reports this form of degeneration in two growths of widely different character: the first described as columnar cell carcinoma was found post mortem in a man of 81, and gave rise to no suspicion during life; the second, composed of spheroidal cells, occurred in a youth of 19, and was extremely malignant, but, owing to the extensive involvement of the neighbouring bowel, its origin in the appendix may be called in question. Apart from Elting's cases the literature supplies no authentic instance of colloid degeneration of growths in the vermiform appendix. In the description of the growth now recorded (p. 458), a process of degeneration was noted which at one stage suggested colloid change, but this did not result in the production of gelatinous masses such as Elting describes.

In the light of these facts it is necessary to consider whether any condition can be found in the appendix which might simulate colloid degeneration. The appendix is richly supplied with mucus-forming cells, and in simple inflammatory conditions large areas of mucoid material are found. A good example of this is recorded by Kelly and Hurdon (p. 283). The two conditions can be differentiated by special mucin stains, but although these might be necessary to distinguish between proliferating glands with increased mucus deposit and a columnar carcinoma undergoing colloid degeneration, in the case under consideration the spheroidal cells exhibit such a degree of anaplasia (if they are derived from Lieberkühn's glands) that they are not likely to possess the mucus-forming function of the original columnar cells.

In comparing the present case with those previously recorded, it is interesting to note the difficulty in determining the starting-point of the tumour, which is felt more especially by the authors who report spheroidal celled growths.

In two instances the following statements respectively occur: (1) 'Not associated with the mucosa' (Case 29). (2) 'Not arising from the mucosa' (Case 31). And although such precision is not commonly employed it is apparent that in many cases the association of the growth with Lieberkühn's glands is the result of inference rather than of ocular demonstration. The submucous coat is replaced by the mass of new growth, while the mucosa appears remarkably intact.

One of the structural features of the appendix is the insignificance of its muscularis mucosae. It is often impossible to recognize this layer which should

be interposed between the mucosa and submucosa. Hence there is no visible demarcation between mucosa and submucosa, and unless serial sections are systematically cut through the whole tumour it is unlikely that the point of origin will be determined.

Again, owing to the tenuity of the muscularis mucosae there is no bar to the direct progress of the growth into the submucosa where it may develop amid yielding aveolar tissue and lymphoid masses and gain access to the main lymphatic channels of the organ.

The problem which arises in connexion with the growth now reported and is peculiarly associated with the type of growth known as spheroidal cell carcinoma of the appendix, must now be considered. How can the clinical history in these cases be reconciled with the histological findings? If these tumours are spheroidal cell carcinomata originating in the columnar cells of Lieberkühn's glands they should be most actively malignant. 'The deviation of the tumour tissue from the normal type towards the round cell in the case of connective tissue tumours and to the spheroidal cell in the case of epithelial cells is now conveniently expressed by the term "anaplasia", and it is possible to express the structural alteration in the form of a law: The degree of anaplasia exhibited by a tumour represents the degree of its malignancy.'[7]

The desire to avoid the discrepancy afforded by the innocent behaviour of tumours so malignant in structure has prompted several suggestions which may be briefly noted.

A. That the appearances are due to inflammation.

This suggestion is usually advanced in a tentative manner and is not supported by histological evidence; but since it is always brought forward when these tumours are under discussion it may be suitably considered here. It is possible that those who propound this view are actuated by the following considerations:—

1. That such an explanation would completely remove an almost inexplicable anomaly.

2. That the vermiform appendix, owing to its anatomical configuration, can sustain a degree of inflammation which would be prevented elsewhere in the alimentary tract by the death of the individual.

3. That for this reason, and also because of the variety of tissues which occupy the walls of the appendix, the microscopic appearances resulting from inflammatory processes may present wide variations which are either unrecognized or wrongly interpreted.

There is no doubt that very different appearances may be correlated with differences in the intensity and duration of the inflammatory process, and some of the more unusual features are well exemplified in the following case described by Kelly and Hurdon:—'J. B., age 56, admitted with an attack of appendicitis, and presenting a mass in the right iliac fossa, gave a history of similar attacks during a period of four years. The appendix was bulbous at the end and so

[7] Bland Sutton, *Tumours simple and malignant*, Lond., 4th ed., p. 298.

thick at the base that the stump could not be inverted in the usual way after amputation. The bulbous end contained a dense rounded mass which resisted the knife and suggested carcinoma. The cut surface presented a uniform fibrillated oedematous structure in which was no trace of the normal layers of the appendix.

'Histological examination.—On the surface was a layer of mucus and cellular detritus mixed with lime salts. Occasionally a single layer of flattened epithelium was found resting directly on the dense fibrous tissue. There were no lymph glands or follicles. The greatly thickened submucosa consisted of oedematous fibrous tissue with fairly abundant fusiform cells and numerous thick-walled blood-vessels. Small round cells and plasma cells were fairly numerous, usually occurring in small clumps. The line of demarcation between the submucosa and circular layers was very indistinct. The individual muscle fibres were separated by oedematous fibrous tissue, swollen and palely stained. The peritoneal layer presented similar changes. At one point groups of proliferating glands were found. These areas were covered with a thick layer of mucus which also filled the gland lumina and in places surrounded the base of the glands, apparently infiltrating the fibrous stroma. The glands were irregularly branched, their epithelium swollen and sometimes several layers thick; the cells were mostly degenerated.'

The reproduction of a section from the growth which accompanied this description suggested a new growth undergoing degeneration. In view of such cases as this it is necessary to remember the protean character of inflammation in the appendix when examining reputed new growths. The contention that if these masses of tissue described as spheroidal cell carcinoma are the products of inflammatory processes they should be encountered more frequently in excised appendices, does not render the question of inflammation wholly unattractive, and in order to obtain some evidence on the point numerous preparations have been made from inflamed appendices, tonsils, and adenoid tissue, but, so far, no results of value have been encountered.

B. On the other hand where the growths have been accepted as carcinomata an attempt has been made to explain their benign course by reference to the form, position and structural peculiarity of the appendix.

The influence of the form and position of the organ on the behaviour of invading growths has already been considered, and further discussion on this point will be of little value until the nature of the growths is established beyond all doubt, and their relation to inflammatory processes accurately known.

The structural peculiarity ascribed to the appendix which was supposed to account for the behaviour of invading growths lies in the arrangement of the lymphatics. Kelly and Hurdon found that the appendix was difficult to inject, and they concluded that owing to a system of valves, present in all except the smallest lymphatic capillaries, the various lymphatic areas of the appendix were isolated from each other, and therefore infections could only

spread with difficulty. Jamieson and Dobson, however, found that the injections passed well from the submucous to the subserous plexus, and that all layers could be injected from the submucosa. They are therefore unable to entertain the idea that an infected area is isolated from the rest of the organ by its lymphatics.

C. A third suggestion, which is based on microscopic examination in some cases, is that the appearances are not those of carcinoma, but are due to the presence of an adenoma or an endothelioma. The frequency of the term 'adeno-carcinoma' in the reports indicates that in many cases the growths possessed a glandular structure, but the detailed descriptions show that they frequently failed to present the essential characteristics of a simple adenoma. Adenomata which develop in glandular organs like the liver or breasts are generally encapsuled, while those which arise in hollow viscera such as the intestine, rectum, or uterus, are more commonly pedunculated. In only one instance is a growth in the appendix described as possessing a capsule (Case 26), and in that case the cell nests were irregular in size and shape and did not possess a lumen. In no instance has a growth in the appendix been described as pedunculated; it might be urged that the narrow lumen of the appendix prevents the development of a pedicle, but the formation of adenomata in the uterus would discourage such a contention. A simple adenoma is usually composed of alveoli regular in shape and size and containing cells which are arranged in a single row round a central lumen. These cells are limited by a basement membrane which is nowhere transgressed. The growths described in the appendix exhibit irregular alveoli filled with masses of polyhedral or round cells; occasionally a lumen is seen surrounded by several layers of cells, but more commonly the alveoli are entirely filled with closely packed cells. In some cases a more uniformly glandular conformation is described but the invasion of the muscular coats by the growth serves to distinguish such growths from the simple adenoma. It appears, therefore, that if the growths under consideration are regarded as adenomata, they present discrepancies no less marked than those entailed by their recognition as spheroidal cell carcinomata.

There remains for consideration the suggestion that these growths are endotheliomata. Some specimens have been recorded as endotheliomata, but when described in detail they are found to possess many of the characters ascribed to the spheroidal celled carcinoma. It is necessary therefore to determine as precisely as possible what are the characters of an endothelioma. Henke states that the classification of certain tumours as endothelioma is based on the theory that the endothelium of the lymph and blood spaces is of connective tissue origin. One of the great peculiarities of endothelial tumours lies in this, that endothelial cells (whether in tumour formation or simple inflammation) can at one point appear to be of connective tissue origin, and elsewhere in the same tumour arrange themselves in strands of epithelial aspect.

Endotheliomata may be classified according to the endothelium from which they arise. Such a classification does not concern the present point at issue, but since lymphendothelioma is the most frequent and characteristic of these tumours it may be employed for the purpose of contrast with carcinoma.

1. At the periphery of a lymphendothelioma is a proliferation of the endothelium of the lymphatic vessels or spaces into slender strands of cubical cells which lie in the connective tissue stroma. These slender strands correspond with the course of the normal lymph channels. They are found only at the periphery of the tumour. At the centre of the tumour, cell masses of a rounded form are found lying in the connective tissue stroma; the result is that if only the centre of the tumour is included in the section it is indistinguishable from alveolar sarcoma, or even alveolar carcinoma, since the presence of intercellular material cannot always be determined.

2. Similar cell strands may be found in small cell carcinoma with a well-marked stroma (e.g. a scirrhus); but if the transition of the cell strands into the true connective tissue cells of the stroma is demonstrable, a diagnostic point in favour of endothelioma is established.

3. When the tumour is hardened in alcohol, in the case of endothelioma the cell masses do not shrink away from the walls of the spaces in which they lie; in the case of carcinoma such shrinking does occur. This point is given as an aid to diagnosis by Henke, and, if it may be relied upon, it supports the supposition that certain of the cases are carcinoma and not endothelioma.

4. The malignancy of endothelioma must naturally vary, since a simple naevus and an angio-sarcoma may be morphologically classified as haemendotheliomata; but, on the whole, lymphendotheliomata, while possessing a local invasive tendency, do not give rise to general metastasis. This is also true of the spheroidal celled carcinoma to a remarkable degree.

The detailed descriptions of the recorded tumours do not, in most instances, justify a definite conclusion as to the respective claims of endothelioma and carcinoma on histological grounds; they merely suggest a resemblance to some of the features just outlined as peculiar to the endothelioma, but this suggestion is strongly reinforced in some cases by the exclusion of the growth from the mucosa.

A certain degree of similarity may also be traced in the growths described under the name of transitional carcinoma; for these growths exhibit at one point columnar cells of epithelial type, and at another point groups of spheroidal or round cells, which may be regarded as representing a high degree of anaplasia in a carcinoma or a reversion to the connective tissue type of cell in an endothelioma.

Finally, the local invasive tendency and aversion from metastatic development displayed by these tumours is certainly suggestive of endothelioma, although the association of a malignant appearance with a clinical benignity does not justify the diagnosis of endothelioma in the absence of further histological confirmation.

Conclusions.

The conclusions deduced from the foregoing observations may be thus summarized:—

1. Tumours which display malignant characteristics from a clinical standpoint are very rarely found in the vermiform appendix.

2. In only five of the reported cases of carcinoma of the appendix did the tumours betray a malignant nature. These cases are Nos. 1, 16, 18, 30, 40. In three of these cases, however, it is difficult to exclude the caecum as the possible site of origin of the growth, i.e. in cases 18, 30, 40.

3. The remaining reported cases of carcinoma of the appendix form a group with the following common characteristics:—

Clinically. (1) A very early age incidence.

(2) An undoubted but undefined relationship with inflammatory conditions.

(3) A complete dissociation from all the gross manifestations of malignant disease, e. g.

i. Invasion of neighbouring organs.

ii. Metastatic development.

iii. Post operative recurrence.

Histologically. Two main types are recognized:—

a. Spheroidal cell.

b. Columnar cell.

But some growths exhibit transition from one type to the other.

Both types display under the microscope a tendency to invade tissues other than that in which they originated. They are thus differentiated from perfectly simple tumours, such as adenomata. Their rate of growth is not readily estimated, but would appear to be slow. They rarely undergo colloid degeneration.

In many cases appearances are described which are comparable to those of an endothelioma. For the diagnosis of endothelioma three data are necessary:—

(1) The exact site of origin of the growth.

(2) The character and arrangement of the cells.

(3) The behaviour of the growth.

Of these three data the last and least important is known to be the same in all cases. The second is inadequately detailed in many reports. The first and most important is very rarely available. Therefore, although the term 'carcinoma' is not in accordance with the clinical manifestations of these growths, there are not as yet sufficient grounds to justify the introduction of any other.

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„ „ *Ibid.*, 1905, 238.
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LIST OF CASES.

A. Cases discovered at Autopsy. Numbers 1–8.

In no case were metastic deposits recorded.
All reported as carcinoma except Case 1 (reported as endothelial sarcoma).
Cases 1, 2, 6, 7, 8 were unsuspected during life.
Cases 3, 4 derived from a post-mortem report on cases of obliterative appendicitis.
Case 5 died of peritonitis of obscure origin.

1. Glazebrook, *Virgin. Med. Monthly*, xxii, 221. (**2**).
2. Mosse et Daunic, *Bull. Soc. anat.*, Paris, 1897, 814. (**4**).
3. } Letulle et Weinberg, *Bull. Soc. anat.*, Paris, 1897, 747. (**5**, **6**).
4. }
5. Wright, *Boston Med. and Surg. Journal*, cxxxviii, 150. (**8**).
6. Letulle et Weinberg, *Bull. Soc. anat.*, Paris, 1900, 374. (**9**).
7. Lartigau, *Med. Rec.*, N. Y., lx, 478. (**20**).
8. Elting, *Annals Surg.*, Lond., xxxvii, 549. (**28**).

N.B.—The numbers in heavy type refer to the numbering in the table drawn up by Rolleston and Jones. Cases not appearing in that table are quoted at length in this paper.

B. Cases which betrayed a malignant character. Numbers 9–13.

Cases 9 and 12 underwent operation for relief of sinus following appendix abscess.
Cases 10 and 13 underwent operation for symptoms of appendicitis.
Case 11 died without operation.

9. Beger, *Berlin. Klin. Wochensch.*, xix, 616. (**1**).
10. A. O. J. Kelly, *Proc. Path. Soc.*, Phila., 1900, 109. (**16**).
11. Whipham, *Lancet*, Lond., 1901, i, 320. (**18**).
12. Elting, *Annals Surg.*, Lond., xxxvii, 549. (**15**).
*13. Ménétrier, *Bull. et mém. Soc. de chir. de Paris*, 1903, xxix, 98.

No. 13.

Sex	Age	Duration and Nature of Symptoms	Extent and Result of Operation	Metastasis	Site and Macroscopic Appearance	Microscopic Appearance
♂	27	4 months. Pain in epigastrium and right iliac region. No vomiting. 2 attacks: the first lasted for 3 weeks.	Appendix removed, leaving stump. 3 months later: Laparotomy, ascitic fluid evacuated, secondary nodule removed from abdominal wall.	Sub-clavicular glands, and nodule in abdominal wall. All developed after first operation.	Appendix thickened, firm, milk white appearance, diffusely invaded by growth. Recurrent growth involved caecum, ascending colon, mesentery and parietal peritoneum.	Sections at different levels in appendix all showed mucous membrane and submucosa replaced by new growth which consisted of large and small agglomerations of irregular polyhedral cells with large oval or round nuclei and occasional nucleoli. Nuclei vesicular, protoplasm scanty, cells closely packed and contour indistinct, stroma very small in amount. Nodule from abdominal wall showed same structure.

C. Cases subjected to operation for appendicitis, acute, chronic, or recurrent. Numbers 14–41.

Cases 19 and 32 were reported as endothelioma, the remainder as carcinoma.

Cases 17, 20, 25, 35, 40 were complicated by abscess formation.

In no case were metastatic deposits found.

In Case 29, three retro-caecal glands were removed, but showed only 'hyperplastic lymphadenoid tissue'. Fourteen days later a thickened portion of caecum was removed, but no sign of growth found therein.

In Case 33 a V-shaped portion of caecum was removed with the appendix.

In Case 37 glands were removed but not examined.

In all other cases operation was limited to removal of the appendix.

Recovery after operation in every case except Case 24, where death ensued from intestinal obstruction [adhesion band] four months later. No sign of recurrence at autopsy.

No recurrence in any case.

Case 16 and 35 under observation for 5 years.
Case 27 under observation for 4 years.
Cases 28 and 40 under observation for 3 years.
Cases 33 and 34 under observation for 2 years.

14. Stimson, *Annals Surg.*, Lond., xxiii, 186. (3).
15. Letulle et Weinberg, *Bull. Soc. anat.*, Paris, 1900, 374. (10).
16. Rolleston, H. D., *Lancet*, Lond., 1900, ii, 11. (11).
17. Giscard, *Toulouse, Imp. St. Cyprian*, 1900, ccclx, 360. (12).
18. Kelly, A. O. J., *Proc. Path. Soc.*, Phila., 1900, 109. (13).
19. Ibid. (female, aged 24). (14).
20. Ibid. (male, aged 19). (15).
21. McBurney, *Med. Rec.*, N. Y., lx, 478. (19).
22. Goffe, *Med. Rec.*, N. Y., lx, 14. (21).
23. Harte and Willson, *Trans. Am. Med. Ass.*, Phila., xx, 228. (23)
24. Ibid. (male, aged 25). (24).
25. Moschcowitz, *Annals Surg.*, Lond., 1903, xxxvii, 891. (25).
26. Ibid. (female, aged 20). (26).

27. Walsham, *St. Barth. Hosp. Reports*, Lond., xxxix. (**31**).
28. Weir, *Med. Rec.*, N. Y., 1903. (**32**).
29. Fiske-Jones and Simmons, *Boston Med. Surg. Journ.*, cli, 566. (**35**).
30. Burnam, *Johns Hopkins Hosp. Bull.*, Baltimore, 1904, xv, 136. (**36**).
31. Battle, *Lancet*, Lond., 1905, i, 291. (**37**).
32. Sargent, *Lancet*, Lond., 1905, ii, 889. (**38**).
*33. Kelly and Hurdon, *Diseases of Vermiform Appendix*, Phila. 1905.
*34. Ibid. (female, aged 24).
*35. Ibid. (male, aged 19).
36. Rolleston and Jones, *Trans. Med. Chir.*, Lond., lxxxix. (**42**).
37. McAdam Eccles, ibid.
*38.
*39. Baldauf, *Albany Med. Ann.*, 1905.
*40.
*41. Barker's case—not previously reported.

No.	Sex	Age	Symptoms	Site and Macroscopic Appearance	Microscopic Appearance
33	♀	30	Recurrent appendicitis 7 years. Pain increasingly severe.	At base. Appendix thickened. Distal end cystic. Proximal end indurated.	Growth infiltrated all coats out to peritoneum. Showed small alveoli lined with columnar cells which often quite filled the lumen.
34	♀	24	Abdominal pain for 2 days.	Near tip. Appendix 5 cm. long, thickened, inflamed—twisted. Mucosa grey and gelatinous—small yellow nodule, 6 cm. in diameter, 1·5 cm. from end.	Slight infiltration of muscularis with lymphoid cells. At site of tumour mucosa replaced by mass composed of connective tissue surrounding collections of epithelial cells.
35	♂	19	Abdominal cramps for indefinite period, signs of acute appendicitis for 10 days—with abscess.	In mid length. Appendix 8 cm. long, thickened, inflamed, adherent. Lumen obliterated at site of tumour, which had penetrated to peritoneum. Small perforation at junction of tumour with distal end. On section, tumour dense white, partly granular, partly fibrillated; mucous surface necrotic.	Small alveoli closely packed with small polymorphous cells having scanty protoplasm and sharply-stained nuclei. All coats invaded; relation of growth to mucosa could not be studied.
38	♂	38	Acute appendicitis.	Appendix inflamed and adherent. Mucous membrane ulcerated near site of growth.	Reported as simple alveolar carcinoma.
39	♂	23	Chronic appendicitis.	Appendix inflamed—lumen obliterated.	Growth consisted of masses of epithelial cells separated by connective tissue—it occupied the submucosa.
40	♀	8	Acute appendicitis with abscess.	Appendix acutely inflamed.	Simple alveolar carcinoma—spreading through submucosa and associated with ulceration.
41	♂	17	12 months' recurrent appendicitis.	Growth 2 inches from tip of appendix, concretions present.	Vide p. 457.

D. Cases subjected to operation for relief of supposed inflammatory conditions in the pelvis. Numbers 42–48.

In all cases the lesion in the appendix was unsuspected before operation.

Recovery ensued in every case. In no case has recurrence been recorded.

42. Hurdon, *Johns Hopkins Hosp. Bull.*, Baltimore, xi, 175. (**17**).
43. Jessup, *Med. Rec.*, N.Y., lx, 289. (**22**).
44. Elting, *Annals Surg.*, St. Louis, xxxvii, 549. (**29**).
45. Norris, *Univ. Penn. Med. Bull.*, Phila., 1903, 334. (**33**).
46. Moschcowitz, *Annals Surg.*, St. Louis, 1903, xxxvii, 891. (**27**).
*47. Landau, *Berlin. Klin. Wochen.*, 1906, xlix, 50.
*48. Cullingworth, *Lancet*, Lond., 1904, ii, 1340.

No.	Sex	Age	Symptoms	Site and Macroscopic Appearance	Microscopic Appearance
47	♀	33	Symptoms of uterine fibroid and salpingitis.	At distal end inflamed appendix contained a small yellowish-white growth.	Growth possessed a very rich stroma and small polyhedral cells in glandular arrangement.
48	♀	31	Curetted 4 years previously. Operation for haemorrhoids 6 months previously. Pain in right side 4 months previously, second attack less severe. Tenderness at McBurney's point. Hard mass on right of uterus depression, vaginal fornix.	Extreme tip of appendix bulbous and contained small nodule which obliterated the lumen. Appendix 1½ in. long. On section, mucosa thickened at tip and showed little injected points. Nodule appeared caseous, but was hard. Peritoneum thickened over tumour.	Reported as spheroidal cell carcinoma.

E. Cases of sarcoma. Numbers 49–52.

In each case the growth was a round cell sarcoma.

Case 49 was well 4 years after operation.

Case 50 died after operation.

Case 51 was thought to have recurrence two years after operation.

Case 52 died from general dissemination of the growth.

49. Warren, *Boston Med. and Surg. Journ.*, cxxxviii, 177. (**7**).
50. Paterson, *Practitioner*, Lond., 1903, lxx, 515. (**34**).
*51. Bernays, quoted in Kelly and Hurdon, *Diseases of Appendix*.
*52. Carwardine, *Brit. Med. Journ.*, 1907, 1771.

No.	Sex	Age	Symptoms	Operation	Site and Macroscopic Appearance	Microscopic Appearance
51	♀	29	12 months' pain in right iliac region. No temperature. Hard tumour felt.	Removal of caecum with appendix.	Basal part of appendix enlarged and firm, infiltration involving adjacent wall of caecum on one side. Distal portion normal and free.	Round cell sarcoma involving all coats of appendix; condition of caecum not stated.
52	♀	45	Pain in right iliac region—diarrhoea—wasting for five months. No pyrexia. Deeply seated swelling at pelvic brim.	Removal of:—Appendix. Caecum. Enlarged lymphatic gland.	Appendix 3½ in. long, hard, very adherent. Club-shaped extremity deep behind the ileo-caecal junction. It was enucleated with difficulty and fractured like a carrot near its base. Caecum and ileum normal.	Growth, uniformly composed of round cells with a little intercellular reticulum, involved whole wall between peritoneum and muscularis mucosae; it showed signs of breaking through peritoneal coat at one place. Regarded as lympho-sarcoma originating in submucous tissue.

NOTE.—Since the completion of this paper, Letulle has published observations upon eleven cases of carcinoma of the vermiform appendix.

In two instances the growth was found after operation for the removal of the appendix (Cases 3, 4). In Case 5 operation was originally directed against the uterine appendages. In Case 8 the appendix was removed for examination because Douglas's pouch was found to be full of gelatinous fluid; the discovery was made during a radical cure for inguinal hernia.

In the remaining seven cases the growth was discovered post mortem.

In Cases 1 and 2 the cause of death is not stated.
In Cases 6, 7, 11, death was due to tuberculosis.
In Case 9 death was due to renal and vascular degeneration in a syphilitic patient.
In Case 10 death was due to acute myelitis.

In no case is recurrence recorded.
Metastatic deposits recorded in Cases 1 and 11.

A. Cases discovered after operation.

No.	Sex	Age	Nature and Duration of Symptoms	Extent of Operation	Site and Macroscopic Appearance	Microscopic Appearance
3	♂	10	In infancy, pain and symptoms indicative of peritonitis. Chronic appendicitis.	Excision of appendix. Complete recovery.	Appendix hard, swollen, adherent to epiploon and iliac fossa. Free end dilated, contained pus and stercoral calculus. Stenosed cancerous portion obliterated to naked eye.	Free end acutely ulcerated, epithelium intact except at apex of ulcer. Lieberkühn's glands separated by inflammatory infiltration. Muscularis mucosae nearly invisible. Submucosa thickened and deprived of fatty glomeruli. Stenosed cancerous portion showed linear fissure on section. Stenosis due to lateral thickening of submucosa infiltrated by cancerous elements. Of muscularis mucosae traces only could be found. Lymphatic follicles on side opposite fissure infiltrated with epitheliomatous tissue.
4	♀	20	Sudden attack of abdominal pain, vomiting, and meteorism seven weeks before the operation.	Removal of appendix.	Extremity of appendix swollen to size of cherry-stone, on section found to contain small mass attached by short pedicle.	Mucosa at tip infiltrated by islets of carcinomatous cells intercalated with some surviving Lieberkühn's glands. Thickened cancerous mucosa rests on recognizable muscularis mucosae. Submucosa also cancerous over corresponding area; enclosed by dense fibro-vascular tracts, between which are colonies of polymorphous epitheliomatous cells. Muscular and subserous layers free from cancer.

No.	Sex	Age	Nature and Duration of Symptoms	Extent of Operation	Site and Macroscopic Appearance	Microscopic Appearance
5	♀	30	Symptoms of disease of pelvic organs.	Removal of appendix.	Cancer of appendix developing at site of old cicatrix of ulcerating obliterative appendicitis. Tumour occupied whole extremity of organ.	Tumour composed of islets of epithelial cells crowded close together; they formed a fibro-cancerous mass distinct from the remainder of the sclerosed and atrophied mucosa. The muscular layers were unaffected. The islets of cancerous cells had forced their way obliquely between the muscular bundles. The cancer had advanced through the interstitial spaces into the interior of the lymphatic vessels, where the cancer cells proliferated or formed an embolism.
8	♀	69	Inguinal hernia, indigestion, constipation.	Radical cure. Removal of appendix.	Appendix had assumed shape of a cornucopia. A quantity of gelatinous fluid was poured out from a cancerous colloid tumour inside the appendix.	The glands, follicles, and muscularis mucosae of the appendix had been replaced by cancerous tissue. A cancerous cyst had ruptured into Douglas's pouch. Internally, the muscular layer showed numerous epithelial vegetations, rich in mucin, constituting an epithelial membrane from which colloid was formed. Between the caecum and the cancerous cyst the appendix showed obliterating fibrosis, the result of ulcerative appendicitis. In the cyst at the free extremity was some mucous débris.

B. Cases discovered post mortem.

No.	Sex	Age	Symptoms	Cause of Death	Site and Macroscopic Appearance	Microscopic Appearance
1	♂	35	—	—	Appendix obliterated at distal end, hard, not adherent to surrounding peritoneum. In meso-appendix colonies of new growth insinuated between adipose cells.	Mucous membrane totally destroyed in obliterated tip of appendix. Cancer developed at centre of cicatrix. Non-cancerous portion had fibrous patch at centre of organ. Cancer chiefly occupied large submucous zone surrounding cicatricial plaque. Submucosa transformed into fibrous tissue encrusted with islets of carcinomatous cells. Near cicatricial fissure masses of larger epitheliomatous cells with carcinomatous alveoli perpendicular to cicatricial fissure. In neighbourhood of muscular layer cancerous colonies increased in extent. Muscular layer only infiltrated in circumscribed area. Internal musculature covered by islets of epithelial cells. External muscular layer deeply infiltrated. Subserous layer normal, but almost encroached upon by new growth.

No.	Sex	Age	Symptoms. Cause of Death	Site and Macroscopic Appearance	Microscopic Appearance
2	♀	?	? ?	Congenital deformity of appendix, end transformed into lump size of small olive — hard, smooth, uniform consistency. Last 2 cm. of appendix obliterated.	Carcinoma originating from congenital adenoma of free extremity. Adenoma:—serous envelope enclosing mass of enormous tubular glands, composed of layers of cylindrical cells provided with single nuclei in which the chromatin fibres run parallel to the axes of their respective cells. Some budding of small cancerous cells appeared in the interglandular spaces. Cancer almost as large as adenomatous mass—developed in centre of appendix in submucous tissue—characterized by infiltration in cellular interstices, with islets of alveoli filled with small abnormal cells richly nucleated. Central patch, representing submucous zone of small extent, presented fibroid appearance. Perivascular connective tissue invaded by carcinomatous fistulous tracts. Cellulo-adipose submucosa invaded, except for quarter of extent. Internal muscular layer invaded by numerous cancerous colonies. External muscular layer normal opposite cancerous mass—infiltrated in other parts.
6	♀	29	Alcoholic history. Atrophic cirrhosis of liver. Chronic tuberculosis of lungs and intestines.	Appendix small, permeable to within 1 cm. of its free end—at this point a small, round, smooth mass, not adherent to peritoneum.	The mucosa, healthy in the rest of the appendix, was unrecognizable in the obstructed portion, and the glands, together with the muco-submucous follicles, had disappeared. The muscularis mucosae was infiltrated with cancerous cells, which penetrated even the subserous layer. At the insertion of the meso-appendix the carcinomatous islets had begun to separate groups of adipose cells.
7	♂	33	Cirrhosis of liver. Pulmonary tuberculosis. Tuberculous ulceration of caecum, colon, and rectum.	Appendix free from adhesions. At distal extremity a small tumour. Peritoneum intact at this level.	Free extremity of appendix completely obliterated by tumour, and converted into a fibro-muscular mass infiltrated by colonies of epithelial cells. The carcinomatous process has come into contact with the thickened subserosa, but has not invaded it.
11	♀	39	Chronic pulmonary, renal, and intestinal tuberculosis.	Appendix free, 7 cm. long. Permeable for 3 cm., remainder obliterated, containing rounded tumour. Appendix formerly ulcerated—more recently in a stenosed part a cul-de-sac of Lieberkühn's glands had evolved new growths with epithelial tracts infiltrating lymphatic canals of appendicular stump.	Carcinomatous islets diverged outside central fibroid cicatrix. Obliteration of lumen followed ulcerative appendicitis. Cancer cells small, round, irregular in form, poor in protoplasm.

No.	Sex	Age	Symptoms. Cause of Death	Site and Macroscopic Appearance	Microscopic Appearance
9	♀	65	Syphilitic nephritis, with uraemia. Aneurism.	At base the cancer ruptured through muscular walls of appendix and fatty glomeruli of meso-appendix, invading Gerlach's valve.	Cylindrical carcinoma with advanced mucoid degeneration of meso-appendix. Two forms in appendix itself: (1) Large cylindrical cells. (2) Exuberant cancer buds, irregular, little ramified, elongated. Colloid degeneration in great abundance. Cancer buds followed course of subserous lymphatics, which, though steeped in mucin, were uninfected. Mucosa of Gerlach's valve swollen to cauliflower formation, with typical epitheliomatous buds.
10	♀	26	Acute myelitis.	Appendix 10 cm. long, adherent to ileo-caecal angle. Permeable to last cm., then obliterated. Small hard ovoid tumour at extremity, transversely showed two zones; one fibroid, the other yellowish and less hard, infiltrating entire wall of appendix.	Epithelial cancer, carcinoma with atypical cells.

EXPLANATION OF FIGURES.

Fig. 1 (obj. = $\frac{1}{2}$). Transverse section showing lumen and portion of growth.

Fig. 2 (obj. = $\frac{1}{6}$). Section showing spaces filled with small spheroidal deeply-staining cells—described as Stage I.

Fig. 3 (obj. = $\frac{1}{6}$). Section showing Stage II. Some of the cellular areas contain a single nucleus, others contain two or more.

Fig. 4 (obj. = $\frac{1}{6}$.) Section showing Stage III. There is general shrinking of spaces and destruction of cells, with increase of fibrous tissue.

FIG. 1

FIG. 2

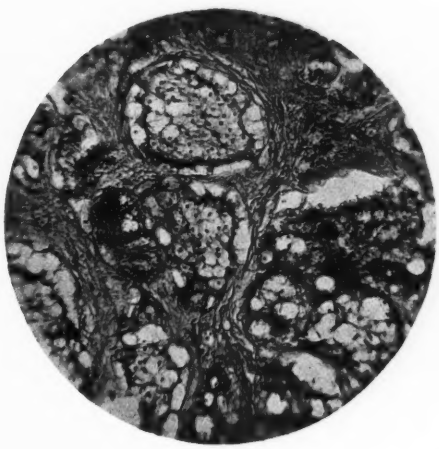

FIG. 3

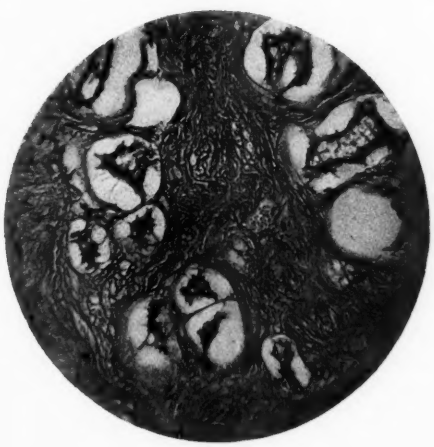

FIG. 4

ON PADS ON THE FINGER-JOINTS

By W. Hale White

With Plates 40–42.

From time to time we see people who have pads upon the dorsal aspect of the joints between the first and second phalanges of the fingers. A. E. Garrod [1] called attention to them in 1893 and 1904. From my own observation I can corroborate all he says about them. They are usually present on some of the joints of both hands, and they may be on all eight joints; but all the joints need not be affected. They vary in size from a split pea to a hazel-nut. Their appearance is well shown in Fig. 1. I myself have never seen them on any other joint, but it is said that very occasionally they may be seen on the terminal phalangeal joints. It need hardly be said that care must be taken when they occur here to distinguish them from Heberden's nodes. They are quite different from these, for they occur at the back of the joint, they are soft, and they can be moved about on the subjacent bone, and do not at all feel as though they were connected with this. They are usually painless, but at times some patients complain of pain and tenderness in them. When once they have formed they are permanent, and they take a few weeks or months to attain their permanent size. Of Garrod's twelve cases, seven were in males, five were in females. Six of the patients had Dupuytren's contraction of the palmar fascia, but the pads nearly always develop at an earlier period of life than the contraction of the palmar fascia. Apart from this association, it is not known that these pads have relationship to any disease. My only justification for publishing a single case is that I am able to supply the first histological account of these pads.

The patient, an officer in the army, was aged 43 when I saw him. He had well-developed Dupuytren's contraction of the palmar fascia of both hands. He first noticed the commencement of this contraction in the left hand two years ago, and it has progressed uniformly since. Eighteen months ago he first observed, on both hands, small lumps on the backs of the joints between the first and second phalanges. A year ago contraction of the palmar fascia of the right hand began; it is now considerable, and of greater extent than that of the left. Fig. 2 shows its condition in the right hand when I saw him. The pads are situated only on the joints between the first and second phalanges. On the right hand there is one the size of a Barcelona-nut on the index-finger; the next finger

[1] A. E. Garrod, *St. Bartholomew's Hospital Reports*, 1893, vol. xxix, p. 157; *British Medical Journal*, July 2, 1904, p. 8.

[Q. J. M. July, 1908.]

has not got one, but on the ring-finger there is one the size of a pea, and on the little finger there is one which is much swollen. On the left hand there is one on the index-finger the size of a small pea, the next finger has one the size of a large pea, the ring-finger none, and the little finger one the size of a small pea. The appearance of these lumps on the left hand is well shown in Fig. 1. The skin over all is movable, and each pad feels to be unconnected with the subjacent bone. That this is so is shown by the X-ray photographs, for which I am indebted to Dr. Hugh Walsham (Figs. 3 and 4). The pads are slightly movable upon the subjacent bone. Each is somewhat soft, indeed sufficiently soft to suggest the possibility that it contains some fluid; but a year ago one had been incised by a doctor, and no fluid was evacuated. The scar of the incision can be seen; it healed perfectly. The patient says that after the incision the lump was a little smaller, but now it is bigger than ever. None of the lumps are painful or tender; there is no evidence that the patient has ever had gout, and, except for the condition of the hands, he is perfectly healthy.

Mr. Charters Symonds excised the palmar fascia of one of the hands, and the patient kindly allowed him to excise one of the pads. A drawing of the microscopical appearances of this, by Dr. T. G. Stevens, is shown in Fig. 5.

It is seen that there is a great hypertrophy of the corneous layer of the epithelium. Considering that these pads, being prominent on the knuckles, must have been subjected to friction, this is what we should have expected. The stratum granulosum is very distinct, and there appears to be nothing abnormal in the rete mucosum. There is no alteration in the papillae, which shows that the pads are not of the nature of corns. The corium appears natural, but under it is a quantity of richly nucleated, not very vascular, fibrous tissue, constituting the tumour. The nuclei and the interlacing bundles of the fibrous tissue are very well seen in the figure. No sweat glands were noticed in the section, and there was no evidence that the tumour was inflammatory. Subcutaneous fibromata, which are very common in various parts of the body, often show inflammatory changes, and these pads do not appear to be a variety of these fibromata. Indeed, they are a pure new growth of fibrous tissue, with some thickening of the stratum corneum; this, however, is probably secondary, and merely due to friction.

EXPLANATION OF FIGURES.

FIG. 1. Shows the pads on the proximal interphalangeal joints of left hand.

FIG. 2. Shows the Dupuytren's contraction of the right palmar fascia.

FIGS. 3 and 4 are X-ray photographs showing that the pads are unconnected with the subjacent joints.

FIG. 5. Shows the histological appearance of one of the pads.

FIG. 1

FIG. 2

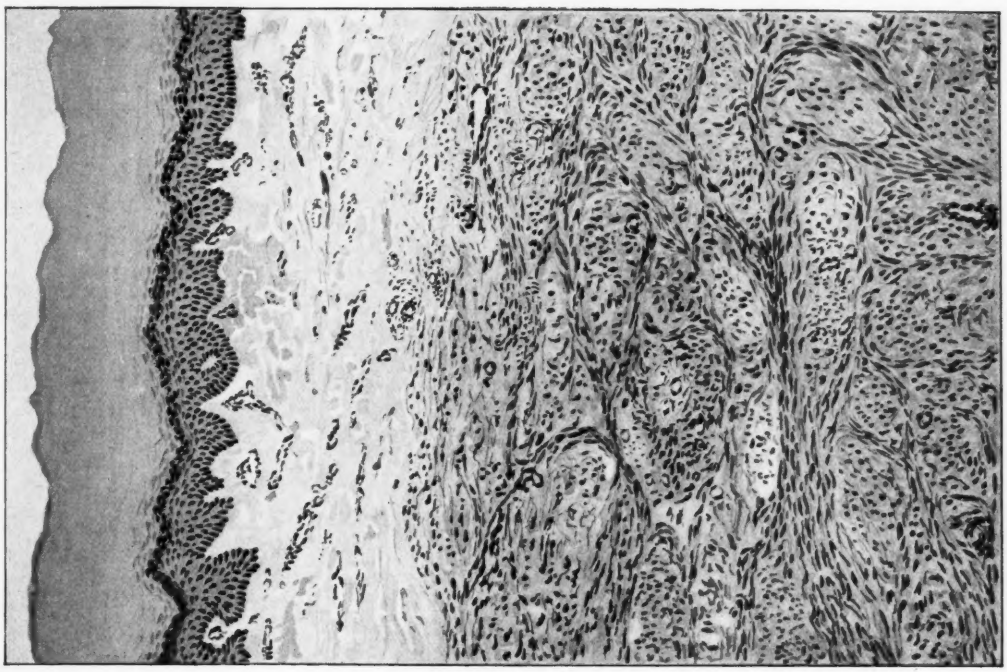

FIG. 5

FIG. 3

FIG. 4

THE EXTRA-SYSTOLE: A CONTRIBUTION TO THE FUNCTIONAL PATHOLOGY OF THE PRIMITIVE CARDIAC TISSUE

By JAMES MACKENZIE

Part II

The clinical features of the extra-systole. The extra-systole is usually recognized by the occurrence of a premature beat in the radial pulse, followed by

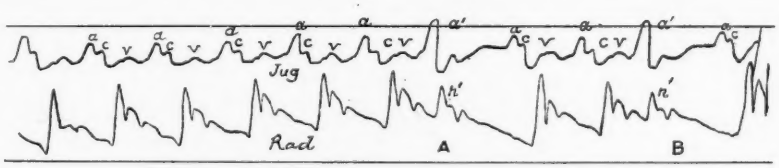

Fig. 1. Shows two extra-systoles (r') followed by a long pause.

an abnormally long pause, as is shown in Fig. 1, where the two small beats (r') are extra-systoles. It may appear only at rare intervals, or it may occur at frequent irregular intervals, or regularly after every 1, 2, 3, 4, or more normal beats.

The force of the ventricular extra-systole may be so weak that no wave is perceptible to the finger in the radial, though it may be detected in the

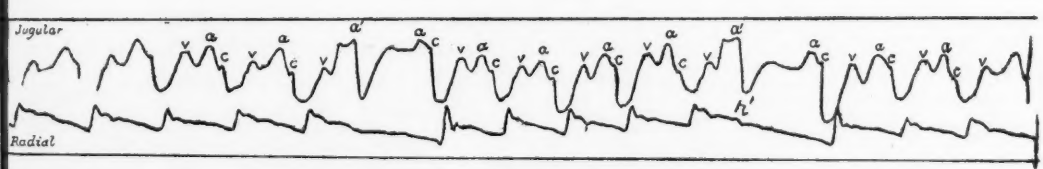

Fig. 2. Shows an extra-systole r' not perceptible to the finger. The jugular pulse (a') during the first long pause in the radial shows that an extra-systole occurred here.

sphygmogram, as r' in Fig. 2. In some cases it may even not appear in the sphygmogram (Figs. 2, 3, and 4), but the heart's sounds, or a tracing of the apex beat at the same time, show that during the long pause in the radial pulse the ventricle contracted, but not with sufficient strength to send a wave into the radial artery. In these cases, if the extra-systole occur regularly after each

normal beat, the pulse at the wrist appears extremely slow, and the case may be put down as 'bradycardia' or heart-block. It may be differentiated by the observation of the jugular pulse (Fig. 13) or apex beat (Fig. 3), or by auscultation.

The extra-systole is easily recognized on auscultation. The regular sequence of sounds is interrupted by two sharp sounds (if very feeble, only one sound may be heard) followed by a long pause. These short sharp sounds represent the first and second sounds of the extra-ventricular systole, and are very characteristic.

Sensations produced by extra-systoles. Some patients are conscious of a quiet transient fluttering in the chest when an extra-systole occurs; others are aware of the long pause, 'as if the heart had stopped'; while others are conscious of the big beat that frequently follows the long pause. So violent is the effect of this after-beat that in neurotic persons it may cause a shock, followed by a sense of great exhaustion. Most patients are unconscious of the irregularity due to the extra-systole until their attention is called to it by the medical attendant.

Prognosis. The most serious thing about these cases is that the consciousness of having an irregularity sometimes makes a patient introspective and depressed. He keeps feeling his pulse, and communicates his doleful tale whenever he finds a sympathetic ear. As the process which gives rise to it in the majority of elderly people is the same as that which produces the tortuous temporal arteries, no more significance should be attached to the one symptom than to the other. I have followed cases for many years, and watched them pass through seasons of sickness and of stress, and have seen no reason to attach any serious import to this symptom. In rare instances, the heart, from being occasionally irregular, has, after many years, become continuously irregular for short or long periods, and in a few the permanent establishment of the nodal rhythm has been the means of hastening the end. But this is infrequent, and in cases of cardio-sclerosis has only happened in advanced life, and the patient should on no account be frightened by being warned of the possible occurrence of this unlikely contingency. In younger and neurotic people I have never seen it lead to any bad results. It may appear in serious affections of the heart, as in febrile complaints, but it does not of itself add to the gravity of the condition, though I am not sure that when due to an acute affection of the heart, as in

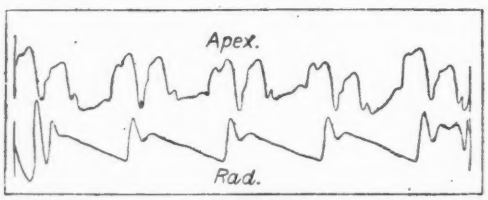

FIG. 3. Shows the presence of an extra-systole in the apex tracing and not appearing in the radial.

pneumonia and rheumatic fever, it may not be a sign of invasion of the myocardium by the diseased process.

Apart from the significance of the extra-systole itself, the manner in which the heart shows associated signs sometimes throws a flood of light on the condition of the heart's functions, and from these very important and far-reaching deductions can be drawn. I have been carefully investigating a number of these changes, but the process is a very intricate one and needs long observation on individual patients. In one line I have taken up I have found many useful signs as to the condition of the heart. This line has been the observation of what happens to a function of the heart muscle, when too little time has been given for that function to recover. Wenckebach has called attention to the fact that unequal recovery of function frequently results in arrhythmia. The application of this principle to diagnosis has been so far regarded as of more scientific interest than practical utility. But it is of much value from a practical standpoint.

Assuming the view I have put forward that extra-systoles are due to a stimulation arising in the remains of the primitive cardiac tube, independently

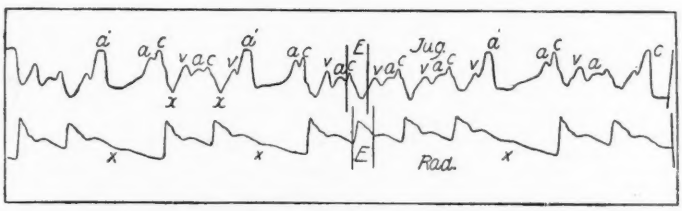

FIG. 4. During the long pauses at *x*, extra-systoles occurred.

of the stimulus normally arising in the sinus, I find that this stimulation may occur under two main conditions: first, in people in whom there seems to be no organic change in the tissue, as in the young and in those in whom extra-systoles appear at intervals and finally disappear, and second, in people of maturer years, in whom it is found associated with sclerotic changes in the heart muscle. In the vast majority of those of the latter class, no gravity can be attached to the condition producing the extra-systole, but in some cases other signs associated with the extra-systole give information from which we can infer the amount of damage done. I have already drawn attention, in the first number of this *Journal*, to the fact that instead of the abnormal stimulation arising occasionally and producing an extra-systole, the heart's contraction may become continuously responsible to this stimulus, for a brief period or permanently—giving rise to the condition I have described as the nodal rhythm. Thus, in Fig. 4 are shown extra-systoles, occurring at *x*, and in Fig. 5 these extra-systoles occur in groups (*v*) due to the abnormal stimulation—the jugular pulse being here of the ventricular type. At times a long series of these beats would continue for minutes, as in Fig. 6.

In some patients the nodal rhythm (groups of extra-systoles) may be transient, and the condition described as paroxysmal tachycardia is so frequently of this nature, that I suggest this term paroxysmal tachycardia should be restricted to transient attacks of the nodal rhythm. If not thus limited the term paroxysmal tachycardia is used to cover such a variety of conditions that it ceases to have any scientific value, and becomes one of those vague and meaningless terms by which medical literature is over-burdened.

From being transient this abnormal rhythm may become permanent, and

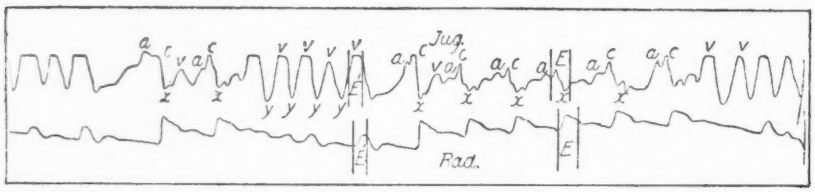

FIG. 5. Groups of extra-systoles occur, producing the waves, *v*, in the jugular tracing, and are of the same nature as those in Fig. 6.

Fig. 6 is from the patient from whom I obtained the tracing Fig. 2. At first the attacks in this case of the nodal rhythm were transient (paroxysmal tachycardia), but it became permanent, and the patient died from the inability of the heart to maintain the circulation with the abnormal rhythm. The post-mortem examination of this heart revealed endarteritis obliterating the artery supplying the bundle, and patches of fibrous tissue affected the muscle wall of the heart and the remains of the primitive cardiac tissue.

Another affection of the *a–v* bundle occurs in heart-block, where fibrous

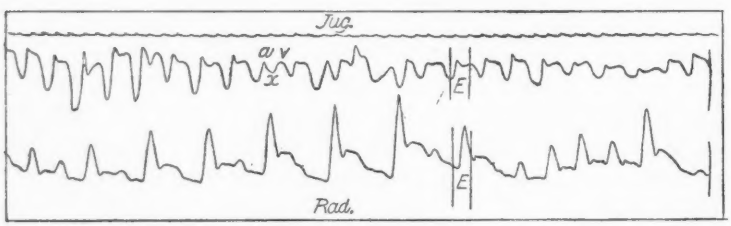

FIG. 6.

changes have been found to break the continuity. One would reason, if my suggestion were correct, that heart-block should be preceded by extra-systoles. I have now had one case where I detected some years ago extra-systoles, and later the nodal rhythm, and, finally, typical complete heart-block with attacks of syncope. In Fig. 7 there is shown a typical auricular extra-systole. If the *a–c* interval (space *A*) be measured it will be found to exceed one-fifth of a minute in duration. The normal *a–c* interval rarely exceeds one-fifth of a second, and when it does so it almost invariably means a delay in the stimulus

passing from auricle to ventricle. When I found the *a–c* interval in this case so distinctly increased, I had no doubt as to the condition being one where the sclerotic process had invaded the *a–v* bundle. I was subsequently shown tracings from this patient, taken some months previously, in which there was undoubted evidence of heart-block.

Another interesting question that arises from considering the signs associated with extra-systole is the reason for the variation in the size of the beats produced by the extra-systole. The reason usually given, viz. that it depends on the quantity of blood in the heart, and on the force of the contraction, is only part of the truth, and there are other factors that have to be considered, so that a very wide field is opened, which has to take into consideration the variation in the size of the beats in all irregular hearts. I do not propose to enter into this matter here, but to call attention to one particular form of variation in the size and strength of the beat which has a most important diagnostic significance.

When one of the functions of the heart muscle is depressed from any cause

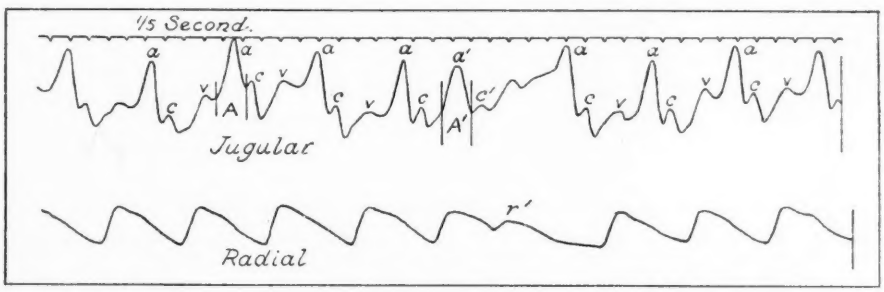

FIG. 7. Shows an *a–c* interval (space *A*) exceeding $\frac{1}{5}$ of a second, and an auricular extra-systole (*a' r'*).

the recovery of the function after its exercise is not so speedy as when the function is normal. Under certain conditions we can demonstrate depression of the function of contraction, by the fact that recovery being slower, the strength of the contraction depends on the length of the preceding beat. The occurrence of an extra-systole in shortening the period of rest at one time and lengthening it at another, gives an opportunity for the function of contraction to display its integrity or its impairment. This question involves the size of the extra-systole, but as so many factors are concerned I do not intend to deal with it here. The long pause after the extra-systole gives the heart time to recover very thoroughly, so that usually the beat after the pause is forcible and sometimes perceptible to the patient. In the radial tracing it is usually of larger size than normal, and in the production of this increased size several factors enter, such as more blood in the ventricle, a lower arterial pressure, and a better recovered contractile force—so that no safe deduction can be drawn from the size of the large beat after the long pause. As, however, this beat is usually stronger it also lasts longer, and in lasting longer it encroaches upon the period of rest immediately

following. By this slight diminution in the period of rest, the following beat may be affected. In healthy hearts the period of rest is so long that a little increase or shortening has no perceptible effect upon the size of the beat, but in damaged hearts a very little variation in the period of rest has a manifest influence on the subsequent contraction. For this reason, in hearts with a good, healthy contractile force, after the first big beat following the extra-systole and the long pause, the size of the beats are fairly uniform. This is not so when there is much exhaustion of the heart muscle. Here the period of rest encroached upon by the long and strong big beat after the pause, does affect the size of the contraction by lessening it, as is well seen in Fig. 8. Here the second beat after the long pause is smaller than any of the subsequent beats. Instead of only the one beat being smaller there may be a regular succession of small and large beats—the *pulsus alternans*—due to the fact that the small beat being shorter in duration, the period of rest following it is longer, so that the next beat is stronger, and being also longer encroaches upon the following period of rest, so that a smaller beat results, and so the alternation goes on. This is seen in

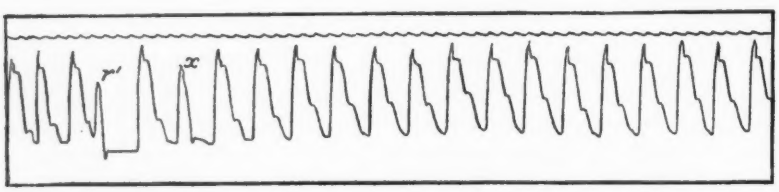

FIG. 8. The small beat r' is an extra-systole. The following beat is big and long on account of the long rest preceding it. Being long it encroaches on the following period of rest, with the result that the next beat x is small and short.

Fig. 14, when after the long pause the alternating character of the pulse becomes more marked.

The reason I dwell upon this is that the appearance of even one small beat after the big beat, as in Fig. 8, is of a very profound significance. While it implies exhaustion of the heart muscle, experience has told me that in people of mature years it is invariably associated with advanced degenerative changes in the heart muscle, and is hence a very valuable sign of myocardial degeneration. It is never seen after the extra-systoles of the young nor in those with a good reserve of force in the muscle wall, though the muscle may be slightly impaired. It is not of necessity a sign of degenerated muscle, being only a sign of exhaustion. Thus Fig. 9 is from a healthy but exhausted heart of a dog. The ventricle was stimulated, and an extra-systole (r') resulted. After the long pause there was a big beat which exhausted the muscle and encroached upon the period of rest, so that the subsequent beat (x) was small—a condition very like that shown in Fig. 8. While the occurrence of the small beat x in Figs. 8 and 9 is merely an evidence of exhaustion when it occurs in elderly people liable to degenerative change in the heart muscle, it may be taken in such people to imply a very serious and permanent damage of the heart muscle. I have

carefully watched a number of patients who showed this tendency to the alternating rhythm, even in such a slight manner as shown in Fig. 8, and in all it betokened great and permanent cardiac weakness. I have now examined a considerable number of hearts post mortem, in which this alternating pulse had been present, and in all there was profound degenerative change in the heart muscle.

Treatment. If the patient is aware of the irregularity he should be assured that there is no cause for alarm. It is useless to attempt to treat the irregularity itself. If in other respects the patient is well then there is no need for any special treatment. If the patient be suffering from conditions which seem to promote the irregularity, such as dyspepsia, the treatment should be devoted to the removal of the predisposing cause. In people with temporary high blood pressure who show extra-systoles, I find plenty of healthy exercise in the open air specially beneficial. When the associated signs indicate changes in the heart

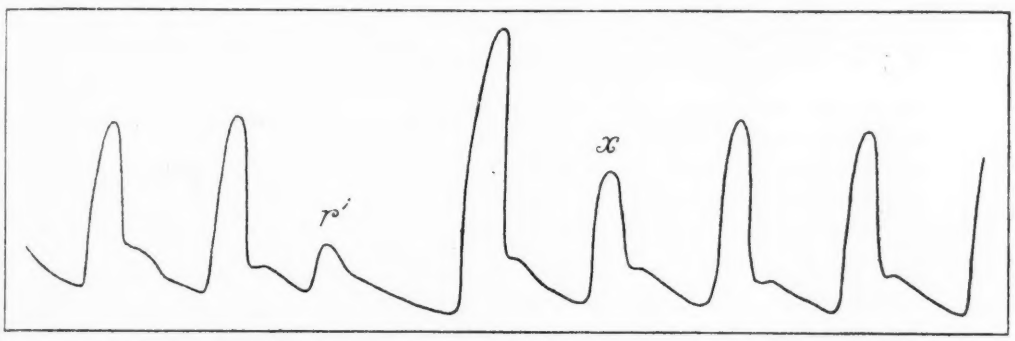

FIG. 9. Tracing from the carotid of a dog. The ventricle was stimulated artificially and produced the extra-systole *r'*. The following beat is big and long and followed by a smaller beat *x*, as in Fig. 8 (Cushny).

muscle, then the lines of treatment should depend on the nature of these changes and not on the extra-systole.

Definition. In the first part of this article I defined extra-systole as 'the premature contraction of auricle or ventricle in response to a stimulus from some other portion of the heart than the sinus, but where otherwise the fundamental or sinus rhythm of the heart is maintained.' I stated that I would deal fully with the reasons that led me to give this limitation to the term.

In the first paper I showed that extra-systoles were due to a premature contraction of the auricles or ventricles, or of auricles and ventricles together, while the fundamental or sinus rhythm of the heart remained unaltered, or occasionally quickened for one beat. It is this dominance of the sinus rhythm, and the occasional independent contraction of auricle and ventricle, that I wish to insist upon as being the essential characteristic of the extra-systole. This

may be considered too narrow a limitation, but it is only by having a restricted and definite meaning to our terms that we are able clearly to appreciate the nature of any phenomena we seek to describe. The reason for this strict limitation of the term is that other irregularities that present a superficial resemblance to extra-systoles are classed amongst them, with the result that the necessity for further inquiry into the real nature of irregularities is not realized.

To illustrate this I cite a few instances from cases of nodal rhythm, heart-

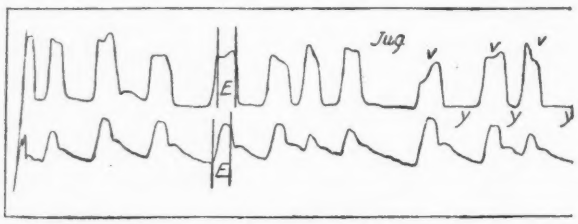

FIG. 10. There is no sign of an auricular wave in the jugular tracing—the venous pulse being of the ventricular form.

block, sinus irregularity, and the *pulsus alternans*, to show how this limitation necessitates further inquiries into other irregularities.

The nodal rhythm. I attempted to demonstrate in the first number of this *Journal* a form of arrhythmia, which I provisionally call the 'nodal rhythm', because I reasoned that the heart's contraction started at the *a–v* node. Sometimes an action of the heart arises, in cases of nodal rhythm, that produces a form of pulse in the arteries very like that produced by an extra-systole. In the paper alluded to, I pointed out that in the jugular pulse of patients with the

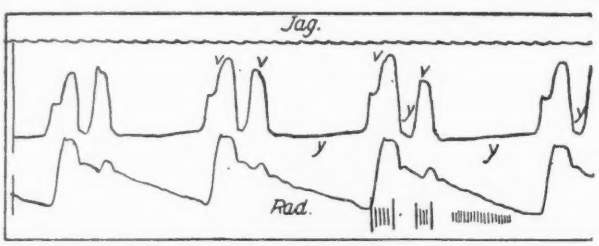

FIG. 11. The small beat in the radial resembles an extra-systole, but the jugular tracing shows no sign of an auricular wave.

nodal rhythm there was never any evidence of an auricular contraction preceding the ventricular, but that both chambers contracted together, or the auricle was 'paralysed'. It will thus be seen that in such a heart there is no fundamental or sinus rhythm, for in the sinus rhythm the auricle responds, and passes the stimulus on to the ventricle. In Fig. 10 the jugular pulse is of the ventricular form, i.e. there is no auricular wave present. The rhythm is continuously irregular. With the administration of digitalis the heart of this patient became

slow (Fig. 11), with a coupling of the beats in such a manner that the radial pulse presented a character very like those of extra-systoles where an extra-systole follows regularly on a normal beat (the *pulsus bigeminus*). If the jugular tracing in Fig. 11 be compared with that in Fig. 12, the difference is so striking that my meaning will at once be clear.

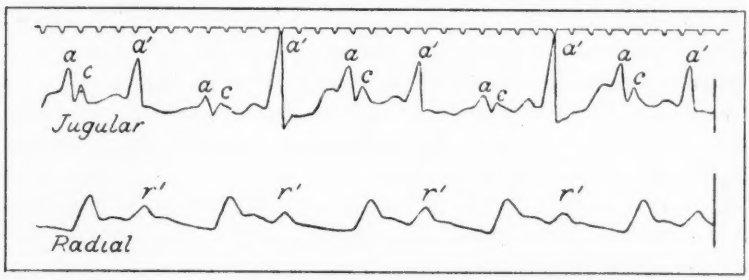

FIG. 12. The small beat in the radial tracing (r') is an extra-systole and the jugular tracing shows a large wave a' at the time of its appearance. The auricle contracts regularly (a and a'), and the large wave a' is due to the fact that at the time the auricle contracted the ventricle was in systole.

In Fig. 12 there are auricular waves (a and a') perfectly regular in time, while the arterial pulse (r') occurs prematurely as seen in the radial tracing. The wave a' due to the auricle is very large, because at the time of its contraction the ventricle was in systole, so that the contents of the auricle could not be emptied into it, and a large quantity is therefore sent back into the veins. In Fig. 13 there is another form of extra-systole—the nodal—where auricle and

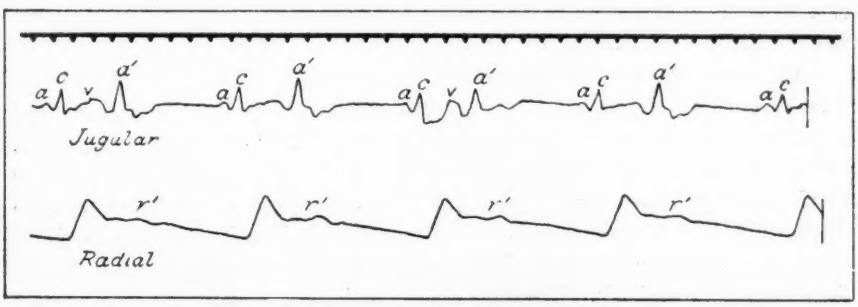

FIG. 13. An extra-systole (r') follows regularly after each normal beat. The jugular tracing shows the participation of the auricle in the irregularity, the auricular wave a' appearing prematurely and at the same time as the ventricular contraction (r').

ventricle contract prematurely and together, as shown by the large wave a', due to the auricle appearing before the normal period. In both these cases the auricle is shown to be present and active, participating in the arrhythmia in Fig. 13 and appearing at its due interval in Fig. 12, where the extra-systole is of ventricular origin.

In Fig. 11, on the other hand, there is no sign of an auricular systole, and

therefore no sinus rhythm governing the heart's action, and the long pause is different here in its nature from the long pause (so-called compensatory pause) in Figs. 12 and 13.

I have only a dim perception of the fundamental nature of the arrhythmia in Fig. 11, but so far as I have inquired into its nature my notions are too speculative to be of any value.

Heart-block. In complete heart-block, when the ventricle pursues its rhythm independently of the sinus or auricle, premature ventricular contractions may simulate extra-systoles, but it is evident that the irregularity resulting is of a different nature from that produced by the extra-systole according to the definition I have given, there being, for instance, no compensatory pause and no dominating rhythm above the ventricle.

Sinus irregularity. The same remark applies to a premature contraction of all the chambers of the heart resulting from a too early contraction of the sinus. In such an instance there is no higher starting-place and an irregularity

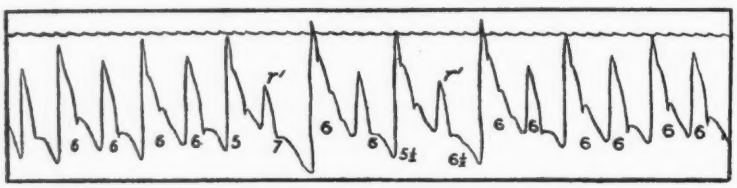

FIG. 14. Characteristic *pulsus alternans*, with two extra-systoles (r'). The numbers represent tenths of seconds, and the period before the extra-systole (r') is shorter, and the period following is larger, than the other periods in the tracing.

of a different kind results, manifested by the absence of a long pause following the premature sinus contraction.

Pulsus alternans. Under certain circumstances every second beat may be a small one, but appearing at the normal time, so that there is a superficial resemblance to the *pulsus bigeminus*, where every second beat is an extra-systole. Both forms of irregularity are shown in Fig. 14, where the smaller beat is regular in its appearance or slightly delayed, except the two beats r'. The numbers in the tracing represent the duration of the cardiac cycle in tenths of a second. It will be seen that the cycle preceding the small waves r' is shorter than normal (5 and $5\frac{1}{2}$), while the cycle following them is larger than normal (7 and $6\frac{1}{2}$)—these being the features characteristic of extra-systole. All the other cycles are practically equal in duration, and the smaller beats have a normal origin, but vary in size for the reason already given. Wenckebach drew attention to the difference between such an irregularity and that due to extra-systole, and very properly has suggested that the term *pulsus alternans* should be restricted to that form of irregularity where the rhythm is regular, but where a small beat and a large alternate. The appearance of extra-systoles with the *pulsus alternans* is a frequent occurrence, and sometimes irregularities of a bewildering variety may be found where they are thus associated.

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